Advances in bronchoscopic lung volume reduction

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Improved patient selection and assessment of treatment response

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CHAPTER 1

General Introduction

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and loss of alveolar structures, causing respiratory symptoms (1). Specific symptoms of this progressive disease can include dyspnea, chronic cough, increased sputum production and increased susceptibility to respiratory infections. COPD is the third cause of death worldwide and claimed 3 million lives in 2016 (2). A prevalence of 600,000 patients in the Netherlands is estimated (3). Tobacco smoking is the most important risk factor for developing COPD, but occupational exposure, air pollution, biomass smoke and genetic predisposition may also contribute (4). COPD can be categorized in a spectrum of phenotypes, including airway disease (bronchitis) and lung parenchymal destruction (emphysema) (1). In patients with the emphysema phenotype, lung parenchyma destruction leads to reduced gas exchange, loss of alveolar attachments to the small airways and diminished protective elastic recoil forces on the airways (figure 1) (1). These structural changes cause increased airway collapsibility, leading to both airflow limitation and airtrapping, thereby causing increased static and dynamic hyperinflation (1).

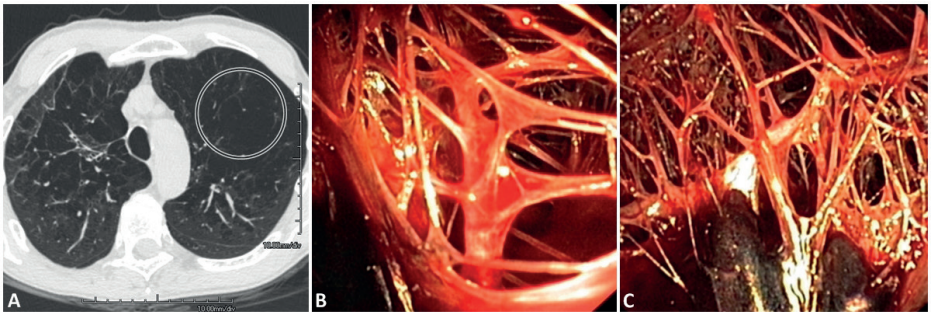

Figure 1: Computed tomography scan of the lung showing severe bilateral emphysema (A). The circle indicates the area that was endoscopically visualized. Transthoracic endoscopic view of the left upper-lobe lung emphysematous parenchyma (B and C). Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Dirk-Jan Slebos, Karin Klooster and Michiel Erasmus. 2012. Emphysema!. AJRCCM. Vol 186, Iss. 2, p 197.

TREATMENT OF COPD

No definitive cure for COPD is available, and all current treatment options for COPD are aimed at relieving symptoms and slowing down disease progression. Treatment options include: smoking cessation, bronchodilators, anti-inflammatory agents, oxygen therapy, pulmonary rehabilitation, vaccination, nutritional support, non-

invasive ventilation and surgical interventions such as lung transplantation, lung volume reduction and more recently bronchoscopic lung volume reduction (BLVR).

The studies in this thesis specifically focus on lung volume reduction techniques. The physiological rationale behind lung volume reduction treatments is that the reduction of static and dynamic hyperinflation reduces dead space, decreases alveolar compression, increases elastic recoil, improves chest wall motion and restores the diaphragmatic function (5).

Lung volume reduction surgery

Lung volume reduction surgery is a treatment for patients with the severe emphysema phenotype of COPD, aimed at reducing lung hyperinflation by resecting the most diseased portions of the lung (6). Lung volume reduction surgery increases the elastic recoil of the lung, leading to improved expiratory flow rates and reduced COPD exacerbations (7,8). The National Emphysema Treatment Trial (NETT), a large multicentre clinical trial in the United States, documented improved exercise capacity, quality of life and dyspnea after lung volume reduction surgery compared to regular medical therapy, but these benefits came at the price of increased short term mortality and morbidity (6). However, the improvement of surgical techniques, strict patient selection and specialized centers may result in lower morbidity and mortality after lung volume reduction surgery (9).

Development of bronchoscopic lung volume reduction techniques

The mixed outcomes of the NETT stimulated the development of several bronchoscopic lung volume reduction treatment techniques. The goal of these techniques is to endoscopically induce collapse of areas of the hyperinflated emphysematous lung, to achieve a beneficial effect similar to lung volume reduction surgery, but without the morbidity of this surgery (6). Different minor invasive bronchoscopic lung volume reduction approaches have been developed and include endobronchial one-way valves, endobronchial coils, lung sealants, steam vapour ablation and airway bypass techniques (10–18). Endobronchial valves and endobronchial coils, the bronchoscopic lung volume reduction approaches that have been studied most extensively, have been demonstrated to both be safe and effective in several clinical trials (10–15). Bronchoscopic lung volume reduction using lung sealants and steam vapour ablation is still in development (16,19). The airway bypass technique has currently been abandoned because of issues with stent patency (18).

PATIENT SELECTION FOR BRONCHOSCOPIC LUNG VOLUME REDUCTION

In order to achieve safe and clinically meaningful results after bronchoscopic lung volume reduction treatment, it is essential to carefully select patients for these treatments. All patients with emphysema who are considered for bronchoscopic lung volume reduction treatment should be on optimal medical therapy, have stopped smoking for at least 6 months and should have completed clinical pulmonary rehabilitation and/or are participating in weekly maintenance physical therapy (20). Other important selection criteria are: increased lung hyperinflation (residual volume (RV) >175% of predicted, RV/Total lung capacity (TLC) ratio >0.58), presence of significant emphysema, and for endobronchial valve treatment, the presence of intact interlobar fissures and thus absence of collateral ventilation.

Previous studies have investigated the reasons for bronchoscopic lung volume reduction treatment ineligibility in clinical practice (21). However, the population referred for BLVR treatment is not yet well characterized in the available literature. Studies investigating which proportion of patients that are referred for BLVR treatment, are actually selected for these treatments are needed to improve future patient selection and referral. In addition, new insights obtained during the development of BLVR techniques, have caused the inclusion and exclusion criteria for these treatments to change over time. For example, the presence of alpha-1 antitrypsin deficiency, a genetic predisposition for developing emphysema was considered a contra-indication for trials investigating endobronchial valves, but these patients are now considered eligible for treatment (10,22).

Lung hyperinflation

All bronchoscopic lung volume reduction techniques are aimed at the reduction of hyperinflation of the lung. The evaluation of lung function is therefore an essential component of patient selection for bronchoscopic lung volume reduction (20). The assessment of hyperinflation can be performed using different approaches, but the most frequently applied methods are body plethysmography and helium gas dilution (23). Body plethysmography is the preferred method to assess RV in patients with severe emphysema, as gas dilution techniques tend to underestimate lung volumes because of airway obstruction and emphysematous destructed areas in the lung with very poor ventilation, preventing the gas to reach all regions of the lung (24). In order to qualify for bronchoscopic lung volume reduction treatment, body

plethysmography testing should demonstrate significant hyperinflation of the lung, defined as RV >175% of predicted and RV/TLC ratio of >0.58 (20).

Interlobar collateral ventilation assessment for endobronchial valve treatment
The purpose of endobronchial valve treatment is to induce lobar atelectasis by occluding all segmental bronchi of a destructed and hyperinflated lobe with one-way valves (20). Endobronchial valve treatment can only be successful in the absence of interlobar collateral ventilation, as the presence of interlobar collateral ventilation prevents the desired lobar atelectasis (10). Collateral ventilation is defined as "the ventilation of alveolar structures through passages or channels that bypass the normal airways" (25).

Collateral ventilation can be assessed using direct and indirect techniques, the direct technique involves the Chartis measurement (Pulmonx Inc., Redwood City, CA, USA), during which a catheter with an inflatable balloon at the tip is used during bronchoscopy to assess the presence of collateral ventilation (26). Indirect techniques to assess collateral ventilation include the use of quantitative computed tomography (CT) analysis to assess interlobar fissure integrity, a predictor for interlobar collateral ventilation (26). The Chartis measurement is started with the inflation of the balloon at the tip of the catheter, allowing for selective occlusion of the lobe to be measured (27). The system is then able to measure expiratory airflow from the occluded lobe, with decreasing airflow over time indicating the absence of collateral ventilation, whilst persistence of airflow suggests the presence of collateral ventilation (27).

Measurement of collateral ventilation using Chartis was initially validated in patients using procedural sedation (28,29). However, given the challenging nature of performing the Chartis measurement under procedural sedation (increased coughing, mucus secretion and difficulties maintaining the right level of sedation), in clinical practice the measurement is also performed under general anesthesia. The effects of the two anesthesia techniques, on the outcomes and feasibility of measurements, have not yet been compared in the literature.

Performing a Chartis measurement can be complicated by the no flow phenomenon, during which a sudden cessation of flow is observed, caused by dynamic expiratory airway collapse, preventing reliable assessment (30).When this occurs in the right lower lobe, measurement of the right major fissure in the right upper lobe is not directly possible because of the presence of the right middle lobe. In these cases,

selective temporary occlusion of the right middle lobe using a blocking device may help in obtaining a reliable Chartis outcome.

Target lobe selection for endobronchial valve treatment

Selection of the most suitable lobe ("the target lobe") for endobronchial valve treatment is based on the degree of emphysema destruction, lobar volume of the target and ipsilateral lobe, heterogeneity between both lobes, absence of collateral ventilation, absence of pleural adhesions and low lobar perfusion assessed using perfusion scintigraphy (20,27,31). Target lobe selection for endobronchial valve treatment can be a challenging task, especially in patients with more than one suitable target lobe or a very homogeneous emphysema distribution. Considering that current target lobe selection is predominantly based on imaging methods that provide indirect information about lung function, there is a need for the development of more direct measurement methods that can aid in target lobe selection (32).

ASSESSMENT OF TREATMENT EFFECT

The assessment of treatment effect after bronchoscopic lung volume reduction can be performed using different approaches: a first approach is to evaluate treatment effect based on change in clinical parameters. These clinical parameters may include pulmonary function tests outcomes, for example forced expiratory volume in 1 second or residual volume, exercise capacity measured using the 6-minute walking test or radiological outcomes such as quantitative assessment of target lobe volume reduction on a chest high resolution CT (HRCT) scan (33–35).

While the evaluation of treatment based on clinical parameters might be the more objective approach, the integration of patient reported outcomes is important as it captures the patients perspective (36). In addition, changes in clinical parameters do not necessarily reflect improvement in symptoms experienced by the patient (37). Finally, some symptoms, such as dyspnea, cannot be assessed objectively (37).

Therefore, a second approach is to evaluate treatment effect based on patient reported outcomes, for example using quality of life questionnaires. One of the most widely used methods to assess quality of life in patients with COPD, is the St. George's Respiratory Questionnaire, which is a validated, self-completed questionnaire (38).

The minimal important difference

After bronchoscopic lung volume reduction treatment, changes in clinical parameters and patient reported quality of life are evaluated by analysing differences in these parameters before and after treatment using statistical tests. However, it is important to assess whether statistically significant changes in outcome parameters are actually meaningful for the patient, since this is not necessarily the case. One method to assess meaningful improvement after treatment is the minimal important difference, which is a threshold value for the clinically relevant change on the individual level; patients who achieve this threshold are considered responders to the treatment (37). The minimal important difference for the St. George's Respiratory Questionnaire has been established previously (39). However, the established minimal important difference might not be applicable for patients with severe emphysema, especially those who undergo bronchoscopic lung volume reduction treatments, as this group was not included in previous minimal important difference calculations.

Radiological evaluation

Radiological evaluation using HRCT scans of the chest is a key element in both the selection of potential bronchoscopic lung volume reduction candidates as well as assessment of treatment effect after bronchoscopic lung volume reduction (20). Quantitative CT analysis may aid in quantifying the severity of emphysematous destruction, distribution of emphysema, lobar volumes and fissure integrity (40). After bronchoscopic lung volume reduction treatment, HRCT scans are performed to assess target lobe volume reduction and to identify potential complications. The currently used, but expert opinion-based cut-off value for target lobe volume reduction is 350ml, however a formal minimal important difference for target lobe volume reduction has not yet been established.

AIMS AND OUTLINE OF THE THESIS

The aim of this thesis is to advance bronchoscopic lung volume reduction treatment in patients with severe emphysema, in particular by improving patient selection for bronchoscopic lung volume reduction treatment and by improving the identification of patients with a meaningful clinical improvement after bronchoscopic lung volume reduction treatment.

In **chapter 2** we review the available literature on the efficacy and safety of lung volume reduction with endobronchial coils in patients with severe emphysema.

In **chapter 3** we investigate a large cohort of patients that was referred to our hospital for assessment of bronchoscopic lung volume reduction eligibility. Our goals are to investigate which proportion of patients that were referred for BLVR were actually selected for bronchoscopic lung volume reduction treatment and to investigate the differences between patients that were selected and not selected for BLVR.

In **chapter 4** the results of a study on the differences in body plethysmography outcomes between patients referred for bronchoscopic lung volume reduction to our hospital and their referring hospitals will be presented, highlighting the importance of dedicated pulmonary function testing.

Chapter 5 describes a study in which we investigate whether a new endoscopic oxygen uptake measurement, designed for identification of the least functional lobe of the lung, can be used as an additional tool supporting target lobe selection for endobronchial valve treatment.

In **chapter 6** and **chapter 7** we investigate in a both retrospective and prospective fashion, the effect of anesthesia technique (procedural sedation versus general anesthesia) on the outcomes and feasibility of endoscopic measurement of interlobar collateral ventilation (Chartis measurement).

In **chapter 8** we present a case series of patients, in which we investigate whether temporary right middle lobe occlusion using a blocking device is helpful to perform a reliable right upper lobe Chartis measurement of the right major fissure, in case of the no flow phenomenon in the right lower lobe.

Chapters 9 and 10 of this thesis are aimed at improving the identification of clinical responders after bronchoscopic lung volume reduction treatment. In order to achieve this goal we re-evaluate the current minimal important differences for the St. George's Respiratory Questionnaire, a frequently used quality of life measurement outcome in patients with COPD (**chapter 9**), and in addition establish a new minimal important difference for target lobe volume reduction after endobronchial valve treatment (**chapter 10**).

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CHAPTER 2

Lung volume reduction with endobronchial coils for patients with emphysema

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ABSTRACT

The lung volume reduction coil treatment is a minimally invasive bronchoscopic treatment option for emphysema patients who suffer from severe hyperinflation. The treatment is aimed at a large group of patients where lung volume reduction surgery and bronchoscopic lung volume reduction using endobronchial valves are no option, or alternatively, can be offered as a bridge to lung transplantation.

The nitinol coil exhibits a shape memory effect and is biologically inert. The lung volume reduction coil procedure is performed in two separate treatment sessions, targeting one lobe per session, with the contralateral lobe being treated 4 to 8 weeks after the first session. In one treatment session, around 10 to 14 coils, thereby treating an entire lobe, are being placed. Selecting optimally treated, symptomatic chronic obstructive pulmonary disease (COPD) patients with emphysema and severe hyperinflation, while avoiding significant airway disease such as asthma, chronic bronchitis and bronchiectasis, is key to achieve treatment success. Three randomized clinical trials investigating lung volume reduction coil treatment have been published until now, reporting the results of 452 treated patients up to 12 months after coil treatment. Lung volume reduction coil treatment results in significant improvement of pulmonary function outcomes and quality of life in patients with severe hyperinflation. The most common complications of lung volume reduction coil treatment are: COPD exacerbations, pneumonia, Coil Associated Opacity and an increased risk of pneumothorax. The purpose of this article is to describe the coil technique and review the available literature regarding effect, safety and future perspectives of lung volume reduction with coils for emphysema patients.

BACKGROUND

Emphysema is characterized by lung parenchymal destruction caused by tobacco smoking, inhalation of other toxic agents, together with predisposed genetic host factors such as α_1-antitrypsin deficiency (1). Lung parenchymal tissue destruction in severe emphysema is associated with increased lung elasticity, loss of elastic recoil, expiratory airway collapse, leading to static as well as dynamic hyperinflation and causing a significant reduction of lung function, exercise capacity and quality of life.

For patients with severe emphysema, the current available treatment options are: smoking cessation, bronchodilators, anti-inflammatory agents, vaccinations, proper nutrition, pulmonary rehabilitation, the use of oxygen, chronic non-invasive

ventilatory support and surgical interventions like lung volume reduction surgery and lung transplantation. Despite all these available treatment options, the majority of patients still remains highly symptomatic or do not qualify for surgical techniques.

Several minimal invasive bronchoscopic treatment options for severe emphysema have emerged, such as endobronchial valves (2), lung volume reduction coils (3) and more experimental techniques such as bronchoscopic thermal vapor ablation (4) and biological lung volume reduction (Aeriseal lung sealant) treatment (5), all aiming at reducing hyperinflation (6). Also very new airway directed treatments such as targeted lung denervation (7) and metered liquid nitrogen cryospray (8) are in development. Hyperinflation is known to play a key role in the feelings of dyspnea and reduced exercise capacity in emphysema (9,10). Targeting this hyperinflation component might significantly relief dyspnea and increase quality of life and exercise performance (2,11).

Depending on appropriate patient selection and correct placement, endobronchial valves reduce hyperinflation which manifests in clinical improvement (12). Responders to valve therapy are only patients with absence of interlobar collateral flow (assessed by quantitative CT fissure analysis, and/or the Chartis® catheter system) between the target lobe and adjacent lobe (2,13,14).

For patients with presence of interlobar collateral ventilation, of which prevalence is estimated to be around 60% in severe emphysema (15), coils might be a potential treatment option (16).

LUNG VOLUME REDUCTION WITH COILS

The coil

The RePneu® coil treatment (RePneu® coil system, PneumRx Inc./BTG, Santa Clara, CA, USA) is a bronchoscopic therapy for the treatment of patients with severe emphysema. The coil consists of a nickel-titanium alloy (nitinol) which exhibits a shape memory effect and is biologically inert (figure 1). The first application in humans was performed in 2008 after extensive testing of the treatment in animal models (17). The coil is produced in 3 different sizes (100/125/150mm) to accommodate different airway lengths.

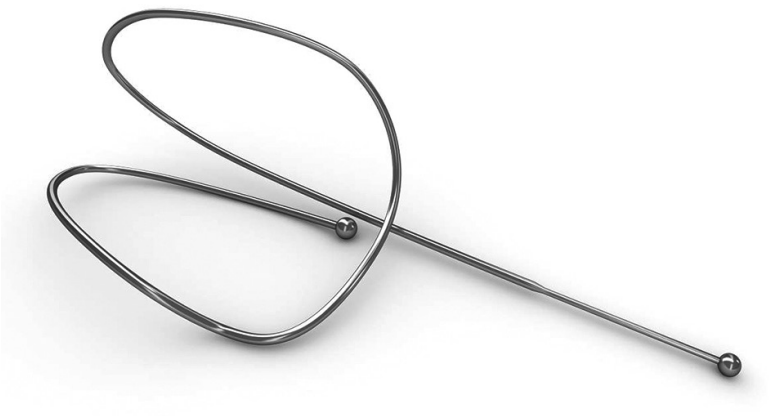

Figure 1: RePneu Coil (125mm); used with permission of PneumRx/BTG.

Treatment procedure

The procedure is preferably performed with the patient undergoing general anesthesia, using a 9mm flexible endotracheal tube with pressure controlled ventilation at a low ventilation frequency (~10/min) with an inspiratory/expiratory ratio of about 1:4 to allow sufficient expiration in these severely air-trapped patients. Normally, patients remain hospitalized one night for regular observation after treatment. All our patients receive both corticosteroids (prednisolone 30mg per day), from the pre-treatment day up to 5 days after treatment, as well as antibiotic prophylaxis (azithromycin 250mg per day) starting on the treatment day up to 30 days post treatment (expert opinion).

The coil placement procedure is, for safety reasons, performed in two separate treatment sessions, targeting one lobe per session, the contralateral lobe being treated 4 to 8 weeks after the first session. Bilateral treatment is necessary to achieve optimal treatment benefit (3). The most diseased lobes should be treated, identified using quantitative CT analysis and when needed perfusion scanning as guidance. Coil placement is performed using a bronchoscope with a therapeutic size working channel (2.8mm internal diameter or larger). It is recommended to take a routine microbacterial culture sample during the first inspection of the bronchial tree, this to be optimally informed about airway colonization, with respect to potential future infectious events.

The coils are delivered, bronchoscopically, into the segmental and subsegmental airways using a special catheter delivery system. Placement is performed under fluoroscopy to visualize positioning and coil sizing (figure 2). The procedure starts with a guidewire, bearing fluoroscopic markers, that is used to measure airway length and to position the coil at a fair distance from the pleura (to avoid pneumothorax and pleural pain). When the guidewire is in the correct position, a delivery catheter can be advanced over the guidewire. The coils are situated in this delivery catheter in a straight configuration. When the target treatment area is reached, the delivery catheter is pulled back and the coil reverts to its non-straightened coil shape, resulting in a compression of the local lung parenchyma. The coil can then subsequently be released.

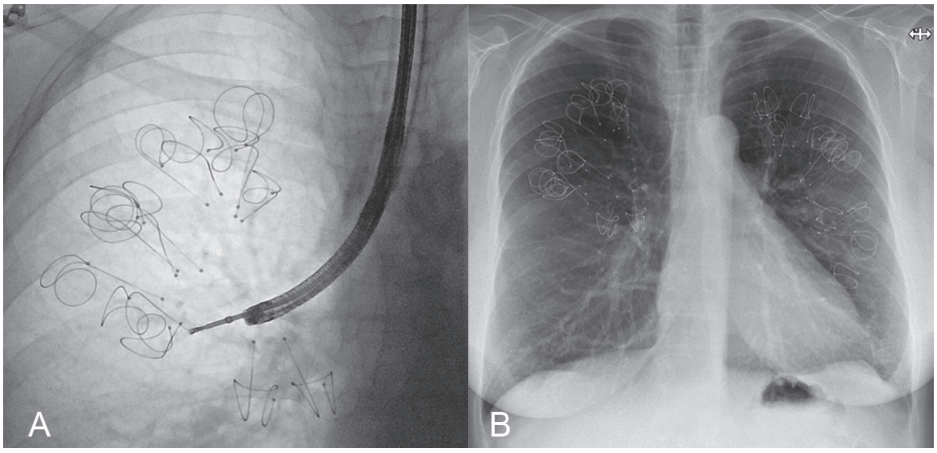

Figure 2: Coil treatment radiological imaging. Panel A: Fluoroscopic image during coil treatment of the right upper lobe in a severe emphysema patient. Panel B: Chest X-ray after treatment with coils.

In one treatment session, around 10 to 12 coils for upper lobes and 10 to 14 coils for lower lobes, are being placed in the desired lobe. During the procedure the coils can be removed and repositioned. The coil treatment is regarded permanent. However, when for example persistent thoracic pain requires removal of one coil, this has been shown feasible up to 10 months after implantation in specialist centers (18).

Mechanism of action

The hypothesized mechanism of action of the coil treatment is that the compression of the lung parenchyma by the coils results in less hyperinflation and simultaneously better transmits the elastic recoil pressure, meaning a real lung volume reduction

effect (19). Secondly, the coils reduce airflow towards the targeted segments of the lung and this consequently results in a redistribution of airflow towards healthier parts of the lung (20). Furthermore, a decrease in airway resistance occurs in the treated lobes (19,21). Finally, the volume reduction of the emphysematous treated areas could improve lung compliance and put the diaphragm in a better condition of function with, as a consequence, an increase in driving pressure of the expiratory flows (19,22,23).

Feasibility & efficacy

An overview of all published original coil studies is presented in table 1.

The first pilot study on coil treatment started in 2008 in Heidelberg (Germany). Eleven patients were treated with up to 6 coils per lobe, demonstrating both feasibility and safety, but no statement on efficacy could be made (17).

The second pilot study started in 2009 in Groningen (The Netherlands). Sixteen patients were treated, demonstrating safety, feasibility and efficacy of the procedure by using the second generation of the coil and increasing the number of coils per treated lobe to 10-12. At six months follow-up after the final treatment, there were significant improvements of -14.9 points ($P<0.001$) in St. George's Respiratory Questionnaire (SGRQ), -11.4% ($P<0.001$) in residual volume (RV), +84.4 meter ($P<0.001$) in 6 minute walking distance (6MWD) and +14.9% ($P=0.004$) in forced expiratory volume in 1 second (FEV_1), compared to baseline (24).

The third study and first randomized controlled trial investigating coils was the RESET trial (Endobronchial coils for the treatment of severe emphysema with hyperinflation). Forty-six patients with both homogeneous and heterogeneous emphysema were allocated in a one-to-one ratio to either coil treatment (treatment group) or best medical care (control group). Patients were treated in two sessions, with the contralateral lobe being treated 1 month after the initial treatment. Outcome measures were performed 90 days after the final treatment or the equivalent visit for the usual care group. Differences between treatment and best medical care group scores in change from baseline were -8.4 points ($P=0.04$) in SGRQ, -0.31L ($P=0.03$) in RV, +63.6 meter ($P<0.001$) in 6MWD and +10.6% ($P=0.03$) in FEV_1 at 90 days follow-up after the final treatment (25).

The fourth study, an open label feasibility study, investigating coils in strict homogeneous emphysema, confirmed the efficacy of treatment for this phenotype. At 6 months follow-up after treatment, there were significant improvements of -15 points (P=0.028) in SGRQ, -0.6L (P=0.007) in RV, +61 meter (P=0.005) in 6MWD and +18.9% (not significant, P=0.102) in FEV_1, compared to baseline (21).

The fifth study, a European open-label feasibility study including 60 patients, confirmed the previously published single center results in a multicenter design with a good safety profile and sustained results up to 12 months follow-up. At 12 months follow-up after treatment, there were significant improvements of -11.1 points (P<0.001) in SGRQ, -0.71L (P<0.001) in RV, +51.4 meter (P=0.003) in 6MWD and 0.11L (P=0.037) increase in FEV_1, compared to baseline (26).

The sixth study and second randomized controlled trial was the REVOLENS trial (Lung Volume Reduction Coil Treatment versus Usual Care in Patients With Severe Emphysema). One hundred patients were allocated in a one-to-one ratio to either coil treatment or usual care. Contralateral treatment took place 1 to 3 months after the first. Approximately 10 coils per targeted lobe were delivered. All patients were assessed at baseline and at 1,3,6 and 12 months after baseline. Differences between treatment and usual care group scores in change from baseline were -13.4 points (P<0.001) in SGRQ, -0.37L (P=0.01) in RV, +21 meter (not significant, P=0.06) in 6MWD and +11% (P=0.01) in FEV_1 at 6 months post treatment (27).

The seventh study and third randomized controlled trial was the RENEW trial (Effect of Endobronchial Coils versus Usual Care on Exercise Tolerance in Patients With Severe Emphysema), including 315 patients. Differences between treatment and usual care group scores in change from baseline were -8.9 points (P<0.001) in SGRQ, -0.31L (P=0.01) in RV, +14.6 meter (P=0.02) in 6MWD and +7% (P<0.01) adjusted median increase in FEV_1 at 12 months post treatment. The greatest improvements occurred in the residual volume ≥225% predicted subgroups, in both heterogeneous and homogeneous emphysema phenotypes, highlighting the importance of the presence of hyperinflation (11).

An overview of efficacy outcomes of the larger studies is provided in table 2.

Table 1: Literature overview of original trials on the lung volume reduction coil treatment for emphysema

Literature overview of original trials on the lung volume reduction coil treatment for emphysema				
Author (publication year)	Title	Patients	Study design	NCT identifier
Herth ***et al.*** (2010)	Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study.	11	Pilot Study	N/A
Slebos ***et al.*** (2012)	Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema.	16	Pilot Study	NCT01220908
Shah ***et al.*** (2013)	Endobronchial coils for the treatment of severe emphysema with hyperinflation: a randomised controlled trial (RESET).	46	RCT	NCT01334307
Deslée ***et al.*** (2014)	Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial.	60	Feasibility Study	NCT01328899
Kontogianni ***et al.*** (2014)	Effectiveness of endobronchial coil treatment for lung volume reduction in patients with severe heterogeneous emphysema and bilateral incomplete fissures: a six-month follow-up.	26	Retrospective Analysis	N/A
Klooster ***et al.*** (2014)	Lung volume reduction coil treatment in COPD patients with homogeneous emphysema: a prospective feasibility trial.	10	Feasibility Study	NCT01421082
Hartman ***et al.*** (2014)	Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema.	38	Retrospective Analysis	N/A
Zoumot ***et al.*** (2015)	Endobronchial coils for severe emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial.	45	Retrospective Analysis	NCT01334307
Deslée ***et al.*** (2016)	Lung volume reduction coil treatment versus usual care in patients with severe emphysema (REVOLENS).	91	RCT	NCT01822795
Sciurba ***et al.*** (2016)	Effect of endobronchial coils versus usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial.	315	RCT	NCT01608490
Hartman ***et al.*** (2017)	The safety and feasibility of re-treating patients with severe emphysema with endobronchial coils: a pilot study.	8	Pilot Study	NCT02012673
Kontogianni ***et al.*** (2017)	Coil therapy for patients with severe emphysema and bilateral incomplete fissures - effectiveness and complications after 1-year follow-up: a single-center experience.	86	Retrospective Analysis	N/A

N/A: Not applicable; NCT: National Clinical Trial Register; RCT: Randomized Clinical Trial.

Table 2: Efficacy outcomes of the main lung volume reduction coil treatment studies

Efficacy outcomes of the main lung volume reduction coil treatment studies					
Study	Slebos 2015 (Meta analysis)[a]		Shah 2013 (RESET)	Deslée 2016 (REVOLENS)	Sciurba 2016 (RENEW)
Follow-up (months)	6	12	3	12	12
n	125	96	T23:C23	T44:C47	T158:C157
	Δ ± SD:		Between-group difference (95% Confidence Interval):		
Δ FEV_1 (liters) (% relative change)	+10.4%[b]	+10.4%[b]	+10.6 (1.1 to 20.1)	+11 (5.2 to ∞)	+7.0 (97.5% CI: 3.4 to ∞))
Δ RV (liters)	-0.51 ± 0.85	-0.43 ± 0.72	-0.31(–0.59 to –0.04)	–0.36 (–0.10 to -∞)	–0.31 (97.5% CI: ∞ to –0.11))
Δ 6MWD (meters)	+44.1 ± 69.8	+38.1 ± 71.9	+63.6 (32.6 to 94.5)	+21 (–5 to ∞) P=0.12	+14.6 (97.5% CI: 0.4 to ∞)
Δ SGRQ (units)	–9.5 ± 14.3	–7.7 ± 14.2	-8.4 (–16.2 to -0.47)	–10.6 (–5.8 to -∞)	-8.9 (97.5% CI: ∞ to –6.3)

95% (one-sided) confidence intervals unless otherwise indicated. P<0.05 unless otherwise indicated. [a] Slebos, 2012; Klooster 2014; Deslée 2014; Zoumot 2015 [b] % Relative change in FEV_1 was calculated because only baseline and change scores were provided in the manuscript. T: treatment group; C: control group; Δ: change between baseline and follow-up; SD: standard deviation; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; RV: residual volume; 6MWD: 6-minute walking distance; SGRQ: St. George's Respiratory Questionnaire.

Safety-profile

The most common complications of coil treatment are: COPD exacerbations, pneumonia, Coil Associated Opacity and an increased risk of pneumothorax (11,25,27).

In a 2015 meta-analysis, including 140 patients, no serious adverse events occurred periprocedural in any of the 259 coil procedures and no deaths or respiratory failures were reported. A total of 37 severe COPD exacerbations and 27 pneumonias requiring hospitalization were recorded among all patients up to 1 year of follow-up. Pneumothorax occurrence for which chest tube insertion was required was 6.4% per patient treated. Severe COPD exacerbation incidence was 3.1% in the first month after treatment, 2.9% per month from 1 month to 6 months after treatment and 2.3% per month from 6 months up to 1 year follow-up. Pneumonia incidence was 3.5% per month during the first month after treatment, 1% from 1 month to 6 months after treatment and 2.1% per month from 6 months up to 1 year follow-up (3).

Coil Associated Opacity, a phenomenon first described by the "RENEW" study investigators, is a noninfectious, localized tissue response that occurs post-coil implantation in approximately 5-10% of cases. Coil Associated Opacity is hypothesized to be induced by stress forces from the coils on lung parenchyma. Patients with Coil Associated Opacity can demonstrate symptoms comparable to infectious pneumonia and this makes it difficult to distinguish between them. A chest radiograph of a patient with Coil Associated Opacity is provided in figure 3. Patients with Coil Associated Opacity exhibited superior 12-month effectiveness outcomes compared to patients without Coil Associated Opacity or pneumonia (11).

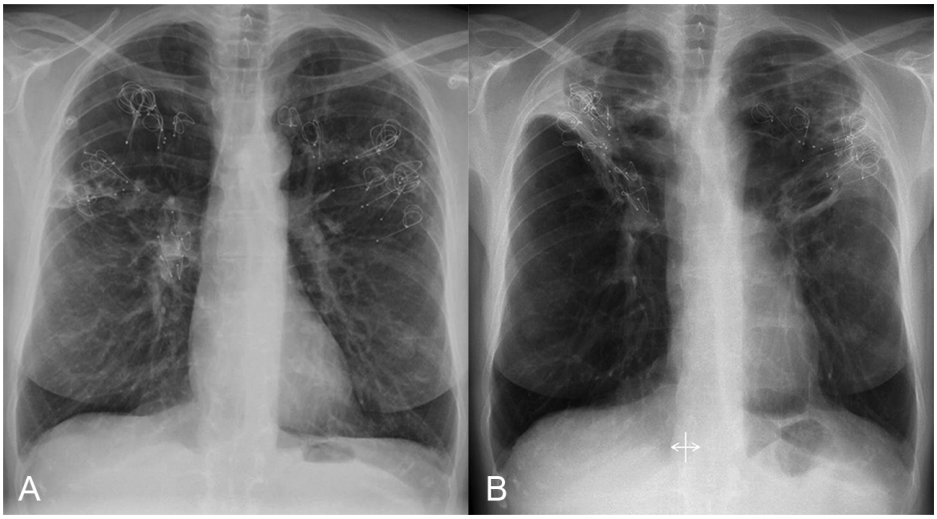

Figure 3: Coil Associated Opacity. Panel A: Post-treatment chest X-ray displaying a mild consolidation around the coil position ("Coil Associated Opacity") in the right lung. Panel B: Chest X-ray 12 months post-treatment in the same patient showing significant volume reduction in both upper lobes due to a post inflammatory fibrotic crowding reaction of the coils resulting in a beneficiary outcome.

Patient selection criteria

Coils are a potential treatment option for patients who do not qualify for endobronchial valve treatment (due to for example positive interlobar collateral ventilation status (16)) or lung volume reduction surgery, and can also be offered as a bridge to lung transplantation. Selecting optimally treated, symptomatic COPD patients with emphysema and severe hyperinflation (absolute minimal criteria for hyperinflation: RV>200% predicted and RV/TLC ratio >58%, measured using body plethysmography), while avoiding significant airway disease such as asthma, chronic bronchitis and bronchiectasis, is key to achieve treatment success (12,28,29). Additional patient inclusion and exclusion criteria specific for the coil treatment from our center are summarized in table 3.

Table 3: In-and exclusion criteria for coil treatment

In- and exclusion criteria for coil treatment	
Inclusion	Exclusion
Severe hyperinflation: Total lung capacity>100% of predicted, and Residual volume>200% of predicted and RV/TLC>58%	Severe hypercapnia (pCO_2 >7.5kPa/55 mmHg) or hypoxemia (pO_2 <6.5kPa/50mmHg)
Post bronchodilator FEV_1<45% of predicted	Post bronchodilator FEV_1<15% of predicted
6 Minute walking distance between 150–450 meters	DL_{CO} <20% of predicted
CT confirmed bilateral emphysema	Chronic bronchitis & asthmatic phenotypes
Optimal disease management: - Stopped smoking - Vaccinations - Nutritious support - Physically fit/post rehabilitation - Optimal medication - Oxygen suppletion when needed - Bilevel positive airway pressure therapy (BiPaP) when needed	Clinically significant bronchiectasis
	Severe recurrent respiratory infections requiring more than 2 hospitalization stays within the past twelve months
	COPD exacerbation within 6 weeks before treatment
	Lung carcinoma or pulmonary nodule on CT scan requiring chest CT scan follow-up
	Giant bulla of more than one third of the lung field on chest CT
	Past history of lobectomy, lung volume reduction surgery, lung transplantation
	Pulmonary hypertension (right ventricular systolic pressure >50mmHg on cardiac echo)
	Significant congestive heart failure
	Alpha-1 antitrypsin deficiency
	Anticoagulants that cannot be permanently stopped
	Allergy to nitinol or one of its components: nickel and titanium

RV: residual volume; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide.

Long term follow-up & re-treatment with coils

To date, not a lot of data exists on longer term outcome after coil treatment. One single center study investigated the safety and efficacy of the coil treatment in the long term at 1,2 and 3 years follow-up. At 3-year follow-up, no long-term unexpected

adverse and device-related events occurred, with clinical benefit gradually declining over time (30).

Re-treatment with coils has been investigated in one pilot study, including 8 patients. Re-treatment was performed at a median of 1382 days after initial coil treatment with a median additional of 12 coils per patient. The trail was not powered for efficacy outcomes. No unexpected adverse events occurred, suggesting feasibility and safety of re-treatment (31).

Cost-effectiveness

Cost-effectiveness of the coil treatment has been investigated in the REVOLENS trial. Cost was estimated at $47,908 per patient above usual care at 1 year and the incremental cost-effectiveness ratio was $782,598 per additional quality-adjusted life-year. However, the short duration of the follow-up prevented the authors from drawing a conclusion on long term cost-effectiveness, as the financial costs of procedure and devices should be allocated over the total duration of clinical benefit. Possibly, the expected 5 year follow-up data from this clinical trial will provide more insight in cost-effectiveness of the coil treatment (27).

CONCLUSIONS AND FUTURE PERSPECTIVES

Three randomized clinical trials investigating coil treatment have been published until now, reporting the results of 452 treated patients up to 12 months after coil treatment. In these trials, the coil treatment results in significant improvements in pulmonary function and especially quality of life in patients with severe hyperinflation.

Since treatment can be performed regardless of collateral ventilation status it may be an effective treatment for patients who are not eligible for endobronchial valve treatment or other collateral ventilation dependent interventions. In addition, both patients with a homogeneous and heterogeneous phenotype can be treated. The selection of optimally treated, symptomatic COPD patients with severe emphysema and severe hyperinflation while avoiding significant airway disease such as asthma, chronic bronchitis and bronchiectasis, is key to achieve treatment success.

Several new studies are currently underway: the first one being the “REACTION study: Identifying REsponders and Exploring Mechanisms of ACTION of the Endobronchial Coil Treatment for Emphysema” (www.clinicaltrials.gov identifier: NCT02179125), a

non-randomised open label multi-center intervention study. The objectives are to gain more knowledge on the mechanism of action, identifying predictors of response and describing the effect on patient-based outcomes of endobronchial coil treatment.

A post-marketing study titled "Changes in Lung Physiology and Cardiac Performance in Patients With Emphysema Post Bilateral RePneu Coil Treatment" (NCT02499380) is aimed at understanding the mechanism of action of the RePneu coil by observing changes in lung physiology and cardiac performance in patients treated with RePneu coils.

Another study: "LVRC-Micro: Lung Volume Reduction Coil Microbiome Study" (NCT03010566), aims to investigate possible changes in the microbiome of the lungs in patients 6 months after initial coil treatment.

An overview of current ongoing studies on coil treatment can be found in table 4.

Future research is necessary to provide more insight in different aspects of the coil treatment. Whilst studies investigating the mechanism of action of the intervention and predictors of response are underway, more work is needed to refine patient selection, assess durability of treatment benefit and determine long term cost-effectiveness.

Table 4: Ongoing studies on lung volume reduction coil treatment

Study title	Trial registry number
Endoscopic Lung Volume Reduction Coil Treatment in Patients With Chronic Hypercapnic Respiratory Failure	NCT02996149
Improvement of Sleep Quality by RePneu Coils in Advanced Pulmonary Emphysema	NCT02399514
Clinical Study to Evaluate the Exercise Capacity in Patients With Severe Emphysema Treated With Coils (CYCLONE)	NCT02879331
Post Market Observational, Prospective, Multi-center Study	NCT01806636
COPD Co-Pilot AIR Substudy of CLN0014 (Co-Pilot Air)	NCT03267992
Lung Volume Reduction Via Coils in Patients With COPD	NCT02246569
LVRC IDE Crossover Study (Crossover From IDE Trial CLN0009) (RENEW-CROSSOVER)	NCT02059057
Hyperinflation Assessment After Treatment by Lung Volume Reduction Coil (HEAT-LVRC)	NCT02835001

NCT: National Clinical Trial Registry Number; COPD: Chronic Obstructive Pulmonary Disease.

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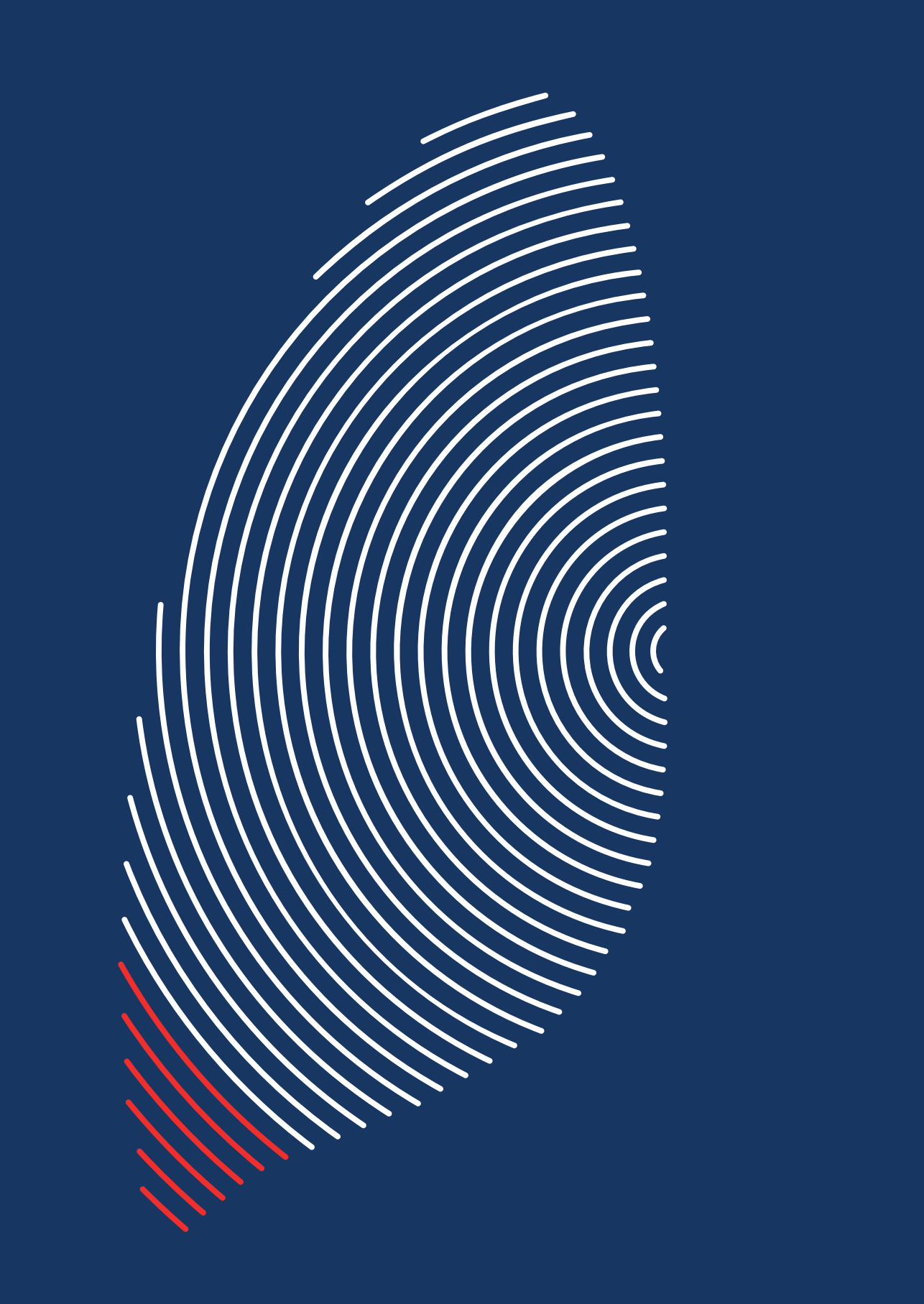

CHAPTER 3

Patient selection for bronchoscopic lung volume reduction

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ABSTRACT

Background: Bronchoscopic lung volume reduction (BLVR) is a valuable treatment option for carefully selected patients with severe COPD. There is limited knowledge about characteristics and outcomes of patients referred to a specialized center for BLVR. The study objectives were to investigate the selection rate for BLVR treatment in patients referred for this treatment, and to investigate the differences between patients that were selected for BLVR and patients that were not.

Methods: We performed a retrospective analysis of patients with severe COPD who were referred to our hospital to assess eligibility for BLVR treatment. Our parameters included demographics, comorbidity, chest computed tomography characteristics, reasons for rejection from BLVR treatment and patient survival.

Results: In total, 1500 patients were included (mean age 62 years, 50% female and forced expiratory volume in 1 second 33% of predicted). Out of this group 282 (19%) patients were selected for BLVR treatment. The absence of a suitable target lobe for treatment, an unsuitable disease phenotype and insufficient lung hyperinflation were the most important factors for not being selected. Patients that were selected for any BLVR option lived significantly longer than the group of patients that were not selected for BLVR (median 3060 versus 2079 days, $P<0.001$).

Conclusions: We found that only a small proportion of patients that are referred for BLVR treatment is eligible for a BLVR treatment, indicating a need for both better referral tools and for the development of new therapies for this group of patients. Furthermore, our data suggest that selection for BLVR is associated with a significant survival benefit.

INTRODUCTION

Bronchoscopic lung volume reduction (BLVR) is a valuable treatment option for patients with severe COPD and emphysema, aimed at reducing hyperinflation of the lung(1). BLVR using endobronchial valves (EBV) and lung volume reduction coils (LVRC) have been studied most extensively and demonstrated to be effective, with an acceptable safety profile (2).

Dedicated patient selection for BLVR is essential in achieving clinically meaningful results after treatment. For example, for the EBV treatment, the absence of interlobar collateral ventilation is necessary to achieve successful outcomes and for the LVRC treatment superior outcomes are observed in patients with very severe static hyperinflation and absence of significant airway disease (3–7).

Several questions on patient selection for BLVR remain unanswered. For example, it is unknown what proportion of patients referred for BLVR is potentially eligible for any form of BLVR treatment and to our knowledge, this group of patients has not been well characterized in the literature. Furthermore, the development of new insights in BLVR treatment during this period led to changes in the inclusion and exclusion criteria for these treatments which potentially could influence the proportion of selected patients.

Therefore, we aimed to investigate 1. which proportion of patients that were referred to our hospital were actually selected for BLVR treatment; 2. the differences in characteristics and survival between patients that were and were not selected for BLVR; 3. to what extent applying updated criteria for eligibility would have affected the selection rate.

METHODS

Study design and patient population

We performed a retrospective analysis of the first 1500 patients who were consecutively referred to assess eligibility for BLVR treatment between March 2007 and October 2014, from 62 different hospitals in the Netherlands to our hospital. Given the retrospective and anonymous nature of the analyses, this research did not fall within the scope of the WMO (Dutch Medical Research with Human Subjects Law) and therefore review by a medical ethical committee was not required.

Evaluation of eligibility

Patient selection for BLVR in our hospital starts with the referral of a patient by their pulmonary physician. Referring physicians are requested to include recent lung function results (spirometry and body plethysmography), chest computed tomography (HRCT) scan, and a complete medical history in their referrals. During a multidisciplinary team meeting, a first selection is made. Potential BLVR candidates are invited to our hospital for a consultation with an interventional pulmonologist.

Treatment

Patients that were eligible for BLVR treatment were included in clinical trials investigating EBV (3,8–11), LVRC (12–15), polymeric lung volume reduction(16), pneumostoma (17–19) and airway bypass stents (20) or in our regular EBV treatment programme (BREATH-NL: NCT02815683).

Outcomes

The primary outcome of this study was the selection rate for BLVR treatment. Secondary outcomes were derived from the referral documentation and included: demographics, lung function (spirometry and body plethysmography), smoking status, oxygen therapy use and maintenance anticoagulant use. Furthermore, the medical history of all patients was screened for a selection of comorbidities. All available CT-scans were visually reviewed and assessed by JBAW for the presence of specific characteristics, these assessments were supervised by DJS.

The degree of emphysema destruction was scored on a 0 to 4 qualitative Likert scale with higher scores indicating more emphysematous destruction (figure 1) (21,22). In case of ineligibility for BLVR, we reported the reasons why patients were found not to be eligible for treatment. The survival status of the referred patients was verified with the Dutch government (Personal Records Database) on June 16th 2019.

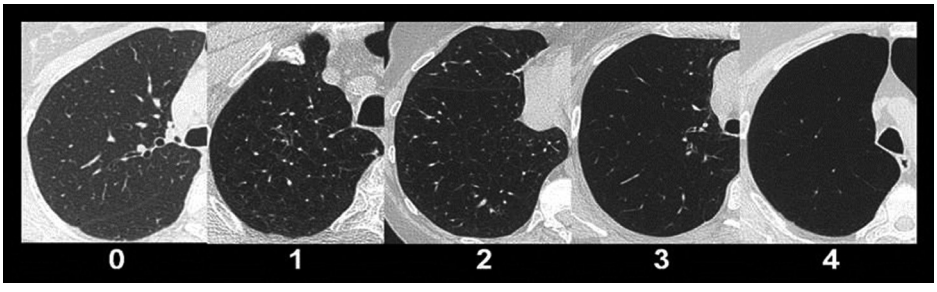


Figure 1: Qualitative scale of emphysematous destruction, scored on a 0 to 4 scale with higher scores indicating more emphysematous destruction.

Theoretical model

We applied some of the most recent inclusion and exclusion criteria for EBV and LVRC, according to the guidelines (1), on our cohort to assess the proportion of patients eligible for these treatments and whether this proportion was different from the proportion of patients actually selected for these treatments. The criteria applied for EBV treatment included forced expiratory volume in 1 second (FEV_1) between 20 and 50% of predicted, residual volume (RV) ≥175% of predicted, RV/total lung capacity (TLC) ratio of ≥0.58, visually intact major fissure (left or right) and emphysema destruction ≥2 on destruction scale (figure 1).

The criteria applied for LVRC included FEV_1 between 20 and 50% of predicted, RV ≥200% of predicted, RV/TLC ratio of ≥0.58 and emphysema destruction ≥2 on the destruction scale (figure 1).

Statistical analysis

Differences in patient characteristics between the group that was selected for treatment and the group that was not, were analysed using an Independent-Samples T-test in case of normal distribution of data and a Mann-Whitney-U test in case of non-normal distribution. A Chi-squared test was used in case of categorical data. Due to the explorative nature of the CT data, only demographic data are presented and no statistical analysis were performed. Survival time was defined as the time after the date of discussion in the multidisciplinary team meeting until the date of verification with the Dutch government. Survival was analysed using the Kaplan-Meier method. Comparison in survival between the groups selected or not selected for treatment was performed using the Mantel-Cox log-rank test and comparison in survival between EBV and LVRC treatment was performed using Breslow's test. All statistical analyses were performed using SPSS version 23 (IBM, New York, NY, USA). P-values <0.05 were considered statistically significant.

RESULTS

In total, 1500 patients (50% female) were included in our analysis, with a mean age of 62 years and FEV_1 of 33±14% of predicted (additional patient characteristics are shown in table 1). From this group, 651 patients (43%) were invited for a consultation in our hospital. Of the total referred population 282 (19%) patients were selected for a clinical trial or regular treatment programme and therefore a total of 1218 (81%) patients were considered not eligible for BLVR (see figure 2 for patient flowchart).

Out of the group of 282 patients that were selected for a bronchoscopic treatment, 175 patients (62%) were selected for EBV, 93 patients (33%) for LVRC, 3 patients (0.2%) for airway bypass stents, 9 patients (3%) for polymeric lung volume reduction and 2 patients (0.1%) for a pneumostoma.

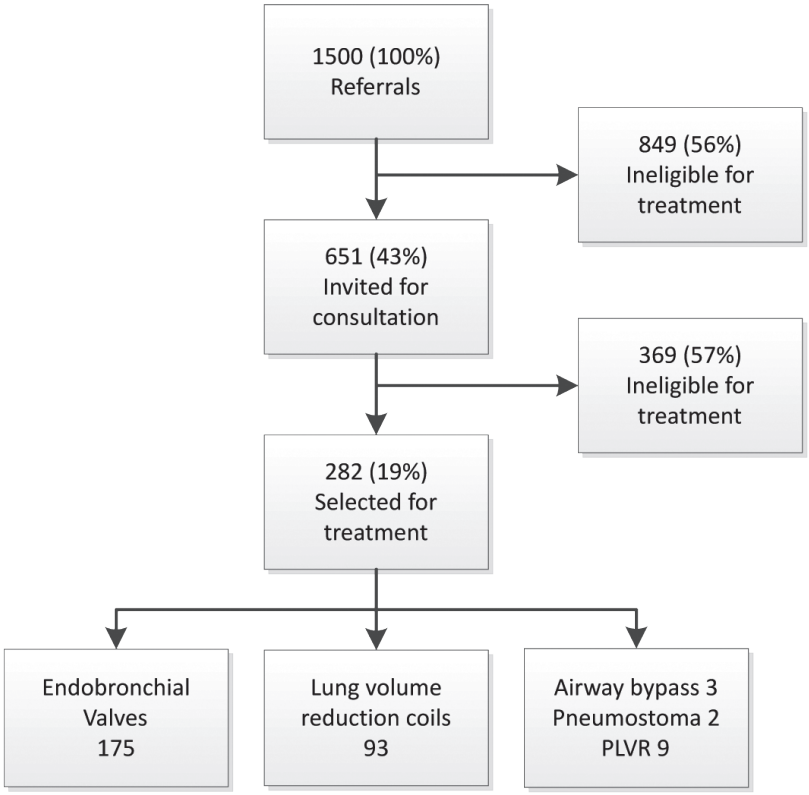


Figure 2: Study flowchart. PLVR: Polymeric lung volume reduction.

Patients selected for BLVR were significantly younger (59 versus 63 years), had a lower FEV_1 (28% versus 34% of predicted) and a higher RV (237% versus 215% of predicted) compared to the group of patients not selected for BLVR (all $P<0.001$).

Table 1: Patient characteristics

	All referrals	Selected for treatment	Not selected for treatment	P-Value
Number of patients	1500	282	1218	
Age (years)	62±9	59±8	63±9	P<0.001
Female (%)	750 (50%)	179 (63%)	571 (47%)	P<0.001
BMI (kg/m^2)	24±5	24±4	24±5	P=0.02
Pack-years (years)	38±18	36±16	38±18	P=0.18
FEV_1 (L)	0.9±0.5	0.8±0.3	1.0±0.5	P<0.001
FEV_1predicted (%)	33±14	28±8	34±15	P<0.001
FVC (L)	2.8±1.0	2.6±0.9	2.8±1.0	P=0.01
FVCpredicted (%)	79±21	77±19	79±22	P=0.08
RV (L)	4.8±1.3	4.9±1.1	4.7±1.3	P=0.03
RVpredicted (%)	219±56	237±46	215±58	P<0.001
TLC (L)	7.8±1.6	7.8±1.5	7.8±1.6	P=0.77
TLCpredicted (%)	130±18	135±15	129±19	P<0.001
Current smoker	123 (8%)	10 (4%)	113 (9%)	P<0.01
Ex-smoker	1051(70%)	263 (94%)	788 (65%)	P<0.001
Never smoker	16 (1%)	2 (1%)	14 (1%)	P=0.52
Unknown	302 (20%)	6 (2%)	296 (24%)	P<0.001
Oxygen therapy	418 (28%)	80 (28%)	338 (28%)	P=0.84
Maintenance anticoagulant use	280 (19%)	44 (16%)	236 (19%)	P=0.14
Participation in previous pulmonary rehabilitation or weekly physiotherapy	684 (46%)	174 (62%)	510 (42%)	P<0.001
Weekly physiotherapy	567 (38%	168 (60%)	399 (33%)	P<0.001

Data are presented as number of patients (%), mean ± standard deviation or percentage of the predicted value ± standard deviation. BMI: Body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity. Differences in patient characteristics between the selected and not selected group for treatment was analysed using a 2-samples T-test or Chi-square test.

The most frequently encountered reasons for ineligibility for BLVR treatment were: absence of a suitable target lobe for treatment (18%), unsuitable disease phenotype for treatment (chronic bronchitis, frequent exacerbations, asthma) (18%) and insufficient hyperinflation of the lungs (16%). See table 2 for the complete list of contra-indications.

The CT scans of 1211 patients (81%) could be assessed, for 289 patients assessment was not possible because of scan unavailability or insufficient image quality for assessment. The proportion of patients with a homogeneous and heterogeneous distribution of emphysema was similar (52% versus 48%). Upper lobe predominant emphysema was observed more often than lower lobe predominant emphysema (71% versus 29%). The left major fissure was found to be visually intact in 44% of patients, the right major in 25% of patients and the right minor fissure in 12% of patients (see table 3).

Table 4 displays the reported comorbidities. Patients referred for BLVR had an average of 1.4 comorbidities and the most frequently encountered comorbidities were hypertension (22%), confirmed or suspected asthma (18%) and coronary artery disease (10%). Patients selected for BLVR had significantly less comorbidities compared to the group of patients not selected for BLVR (1.1 versus 1.4, $P<0.01$).

The survival status of 1272 patients (85%) could be verified. The overall median survival was 2316 days (95%CI: 2146-2485 days). The median follow-up was 2351 days (95%CI: 2451-2514 days). Patients that were referred to our hospital but were not invited for consultation had a median survival of 1808 days (95%CI: 1622-1994) and patients who were invited for consultation but who were not selected for treatment had a median survival of 2524 days (95%CI: 2234-2814). Patients that were selected for BLVR lived significantly longer than the group of patients that was not selected for BLVR (median 3060 versus 2079 days, $P<0.001$), see figure 3. No significant survival difference was observed between patients who were selected for EBV treatment and those who were selected for LVRC ($P=0.45$).

Table 2: Contraindications in patients not selected for BLVR

Contraindication	Prevalence
Number of patients	1218
Number of contraindications Mean ± standard deviation Median (range)	1.3±0.9 1 (0-5)
Absence of suitable target lobe for treatment	221 (18%)
Unsuitable disease phenotype (chronic bronchitis, frequent exacerbations, asthma)	219 (18%)
Insufficient hyperinflation of the lungs	197 (16%)
Presence of comorbidity	162 (13%)
Homogeneous distribution of emphysema	125 (10%)
Incomplete interlobar fissures	109 (9%)
Patient renounced treatment	95 (8%)
Pulmonary function testing outcomes not meeting minimum hyperinflation and/or airway obstruction requirements	95 (8%)
No trial available at moment of evaluation	94 (8%)
Low degree of emphysema destruction	83 (7%)
Did not stop smoking for >6 months	79 (7%)
Did not yet participate in pulmonary rehabilitation	73 (6%)
Maintenance anticoagulant use	54 (5%)
Too high degree of emphysema destruction	53 (4%)
Presence of bullae	47 (4%)
Paraseptal emphysema phenotype	47 (4%)
High level of exercise capacity	43 (4%)
Suspicious nodules in the lung that require follow-up	38 (3%)
Too poor condition for treatment	35 (3%)
Prior thoracic surgery	31 (3%)
Body mass index too high or too low	26 (2%)
Pulmonary Hypertension	22 (2%)
Alpha-1 antitrypsin deficiency	15 (1%)
Lung transplanted before BLVR treatment	3 (0.2%)

Data are presented as number of contraindications (percentage of patients with contraindication), mean ± standard deviation, median (range). BLVR: Bronchoscopic lung volume reduction.

Table 3: CT Characteristics

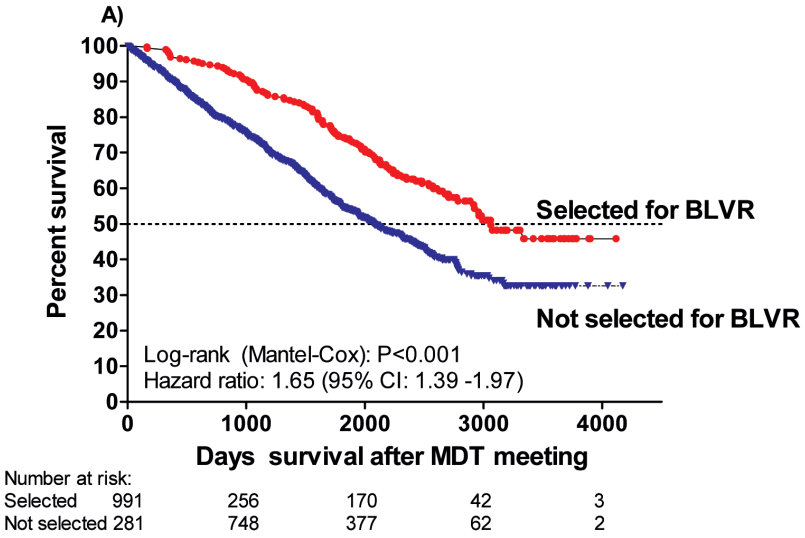
	All referrals	Selected for treatment	Not selected for treatment
Number of patients	1500	282	1218
Scans available	1211	274	937
Mild centrilobular	428 (35%)	80 (29%)	348 (37%)
Severe centrilobular	440 (36%)	113 (41%)	327 (35%)
Panlobular	189 (16%)	66 (24%)	123 (13%)
Paraseptal	146 (12%)	15 (6%)	131 (14%)
No emphysema	8 (0.7%)	0 (0%)	8 (1%)
Distribution homogeneous/heterogeneous (%)	48/52	31/69	53/47
Upper/lower lobes predominant (%)	71/29	64/36	75/25
Destruction LUL 1/2/3/4 (%)	40/38/19/2	35/46/19/1	42/35/19/3
Destruction LLL 1/2/3/4 (%)	55/31/11/1	52/33/13/2	56/31/10/1
Destruction RUL 1/2/3/4 (%)	37/35/24/3	33/39/26/2	38/34/23/3
Destruction RLL 1/2/3/4 (%)	56/32/10/1	53/32/13/2	56/31/9/1
Left major fissure (intact/>90%intact/<90%intact/unknown (%)	44/26/29/2	58/20/22/0	40/28/31/2
Right major fissure (intact/>90% intact/<90% intact/unknown (%)	25/32/41/1	36/31/33/0	22/33/44/2
Right minor fissure (intact/>90% intact/<90% intact/unknown (%)	12/14/72/3	12/18/70/0	11/13/72/3
Bronchopathy	666 (55%)	140 (51%)	526 (56%)
Mild bronchiectasis	151 (13%)	30 (11%)	121 (13%)
Severe bronchiectasis	20 (2%)	1 (0.4%)	19 (2%)
Giant bullae	195 (16%)	21 (8%)	174 (19%)
Nodules requiring follow up	89 (7%)	27 (10%)	62 (7%)
Fibrosis	23 (2%)	2 (0.7%)	21 (2%)
Pleural pathology	13 (1%)	2 (0.7%)	11 (1%)
Suspect for pulmonary hypertension	148 (12%)	25 (9%)	123 (13%)

Data is presented as number of patients (percentage of patients) or as percentage of cases. CT: computed tomography; LUL: left upper lobe; LLL: left lower lobe; RUL: right upper lobe; RLL: right lower lobe. Destruction score based on a 1 to 4 Likert scale, with higher scores indicating more severe emphysematous destruction.

Table 4: Comorbidities reported in the referral documentation

Comorbidity	All referrals	Selected for treatment	Not selected for treatment
Number of patients	1500	282	1218
Number of comorbidities*			
mean±standard deviation	1.4±1.4	1.1±1.2	1.4±1.5
median (range)	1 (0-11)	1 (0-6)	1 (0-11)
Hypertension	323 (22%)	72 (26%)	251 (21%)
Confirmed or suspected asthma	270 (18%)	58 (21%)	212 (17%)
Coronary artery disease	153 (10%)	16 (6%)	137 (11%)
Dyslipidemia	117 (8%)	20 (7%)	97 (8%)
Diabetes	112 (8%)	15 (5%)	97 (8%)
Osteoporosis	105 (7%)	19 (7%)	86 (7%)
Obesity (BMI>30)	105 (7%)	12 (4%)	93 (8%)
Atrial fibrillation	84 (6%)	4 (1%)	80 (7%)
Myocardial infarction	82 (6%)	6 (2%)	76 (6%)
Cerebrovascular incident	76 (5%)	12 (4%)	64 (5%)
Alpha-1 antitrypsin deficiency	70 (5%)	16 (6%)	54 (4%)
Peripheral artery disease	59 (4%)	6 (2%)	53 (4%)
Heart Failure	54 (4%)	5 (2%)	49 (4%)
Depression	54 (4%)	11 (4%)	43 (4%)
Pulmonary embolus	48 (3%)	10 (4%)	38 (3%)
Pulmonary hypertension	46 (3%)	1 (0.4%)	45 (4%)
Gastro-oesophageal reflux disease	43 (3%)	7 (3%)	36 (3%)
Degenerative joint disease	38 (3%)	4 (1%)	34 (3%)
Anxiety	35 (2%)	7 (3%)	28 (2%)
Obstructive sleep apnea syndrome	33 (2%)	5 (2%)	28 (2%)
Gastric ulcer	24 (2%)	2 (1%)	22 (2%)
Pulmonary malignancy	21 (1%)	2 (1%)	19 (2%)
Anemia	20 (1%)	0 (0%)	20 (2%)
Chronic kidney disease	15 (1%)	0 (0%)	15 (1%)
Pulmonary fibrosis	10 (0.7%)	0 (0%)	10 (0.8%)
Liver cirrhosis	2 (0.1%)	1 (0.4%)	1 (0.1%)

Data are presented as number of patients (percentage of patients), mean ± standard deviation or median (range). Differences in the number of comorbidities were assessed using Mann-Whitney-U test. *P<0.01. BMI: Body mass index.



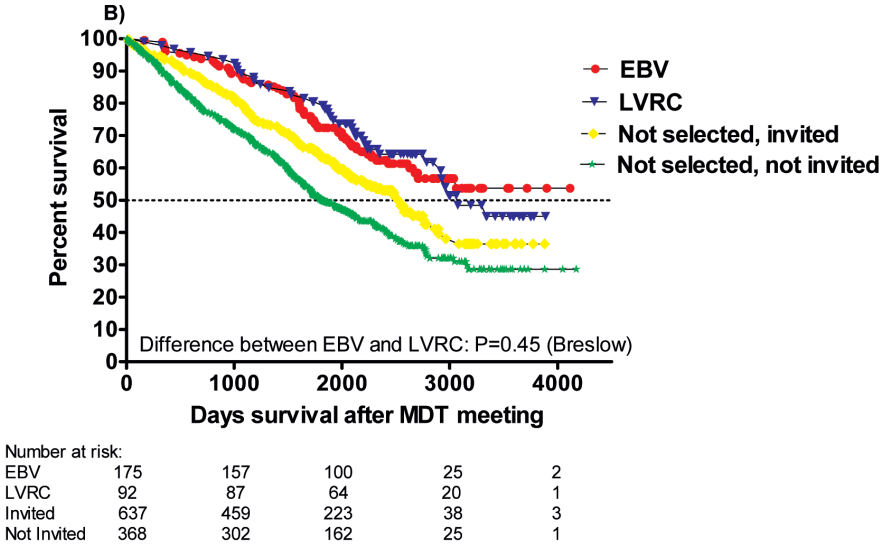


Figure 3: Kaplan Meier plots of survival. Plot A: Survival of the patients that were selected for treatment and the patients that were not selected for treatment. Plot B: Survival of the patients that were selected for EBV, selected for LVRC, invited to our hospital for consultation but not selected for BLVR, not selected for BLVR and not invited to our hospital for consultation. EBV: endobronchial valve treatment; LVRC: lung volume reduction coil treatment; BLVR: bronchoscopic lung volume reduction; MDT: multidisciplinary team meeting.

Theoretical model

When applying some of the currently established inclusion and exclusion criteria for endobronchial valve treatment and lung volume reduction treatment, we identified 283 patients eligible for EBV treatment (19%) while 175 patients (12%) were actually selected for EBV in this cohort and 144 patients (10%) would currently be eligible for LVRC while 93 patients (6%) were actually selected for LVRC (figure 4).

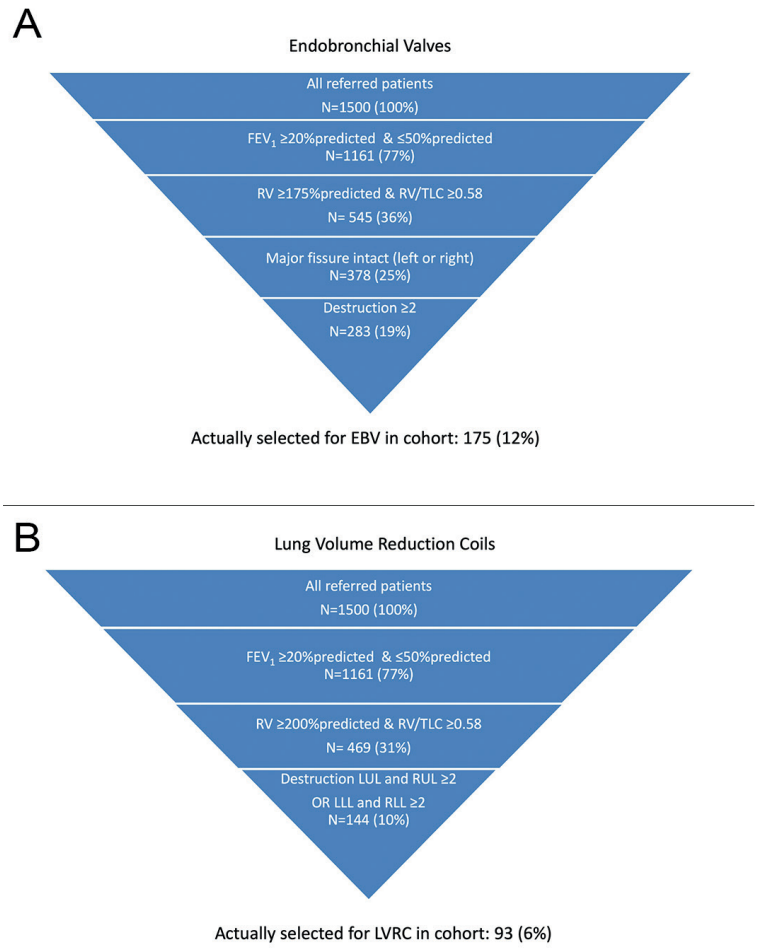


Figure 4: Eligibility for EBV and LVRC after application of current inclusion and exclusion criteria. Panel A: Eligible patients for EBV treatment. Panel B: Eligible patients for LVRC treatment. N: number of patients; FEV_1: forced expiratory volume in 1 second; RV: residual volume; TLC: total lung capacity; EBV: endobronchial valve treatment; LUL: left upper lobe; RUL: right upper lobe; LLL: left lower lobe; RLL: right lower lobe; LVRC: lung volume reduction coil treatment.

DISCUSSION

Only one out of five patients who were referred for BLVR treatment to our hospital were selected for BLVR treatment. Ineligibility for BLVR treatment was most often caused by: the absence of a suitable target lobe for treatment, an unsuitable disease phenotype for treatment and insufficient lung hyperinflation. Overall survival in the group of patients referred for BLVR was poor with a median survival of approximately 6 years.

To our knowledge, this is the largest study investigating patients referred for BLVR eligibility assessment. In a recent study by Polke et al, who studied patients that were referred to a BLVR expert center in Heidelberg (Germany), a higher proportion of patients were found to be eligible for BLVR treatment, possibly caused by a more strict preselection of patients for referral (23). The same study also found the absence of a suitable target lobe to be the most frequent contra-indication for BLVR, which is in line with the results of our study (23).

Only a small proportion of the already preselected group of patients that were considered to be eligible for BLVR by the referring physician is selected for BLVR treatment. This highlights both the need for improved referral strategies on the one hand, and the important need for additional therapeutic options for patients with severe COPD on the other hand. Alternative interventions for BLVR include lung volume reduction surgery or lung transplantation, however both treatments suffer from huge limitations related to the invasiveness of the procedure, scarce availability and strict selection procedures. Patients with a severe chronic bronchitis phenotype of COPD are a common example of an unsuitable disease phenotype for BLVR. Both endobronchial treatment with liquid nitrogen cryospray and targeted lung denervation are currently under development for this phenotype. Liquid nitrogen cryospray is a treatment aimed at inducing an airway tissue healing effect by destroying the hyperplastic goblet cells and excess submucous glands (24). Target lung denervation is a treatment designed to decrease airway resistance and mucus hyper section, by inhibiting parasympathetic pulmonary nerves, using radiofrequency ablation therapy (25).

New insights in BLVR treatment caused inclusion and exclusion criteria for these treatments to change over time, which might have affected the proportion of patients considered eligible for BVLR. For example, a previous contra-indication for EBV trials included the presence of alpha-1 antitrypsin deficiency, but these patients

are now considered eligible for treatment (3,26). When we applied the most recent inclusion and exclusion criteria on our cohort, we observed a discrepancy between the number of patients that were eligible for treatment and those who were actually selected for treatment. This could be the result of the fact that not all treatments were available at all times during the time frame of this study, the clinical trial context with strict in and exclusion criteria or because we applied only a selection of the most stringent criteria in our model.

A significant survival benefit was observed for the group of patients that was selected for BLVR treatment, when compared to the group that was not selected for treatment. This survival benefit was already observed in several previous studies which demonstrated that when successful lobar atelectasis is achieved after EBV treatment, patients have a substantial, persisting survival benefit (27–29). Structural survival data for the LVRC treatment is not yet available. We acknowledge that the survival benefit observed in the group of patients that were selected for treatment might have not only been due to a direct result of the actual intervention but also caused by the exclusion of patients that were too frail, due to any cause, for treatment. On the other hand, both the degree of hyperinflation and airway obstruction were higher in the group selected for treatment, suggesting selection of patients with severe disease for treatment. In addition, given that most treatments in this cohort took place in the early phase of the development of these treatments, the current data might actually underestimate the survival benefit of these treatments.

Patient selected for BLVR had significantly less comorbidities than patients who were not selected for BLVR. On average, the referred patients had more than one comorbidity. However, this was still lower than in a study by Putcha et al, possibly caused by the underreporting of comorbidities by the referring physicians in our cohort or because of the fact that the referring physicians already referred a preselected population due to study selection criteria on comorbidity (30,31).

We assessed the CT characteristics of the referred patients and found the left major fissure to be most often intact on the CT scans of the referred patients, followed by the right major fissure and the right minor fissure. The proportion of visually intact fissures was in line with previously published data on this topic, and also in agreement with the latest clinical trials investigating EBV and intrabronchial valves, in which the left upper and left lower lobe were selected for treatment in more than 75% of cases (11,32,33).

This study has several limitations: first of all, our population is representative of the group of patients referred to a BLVR center but not of the total population of patients with severe emphysema, and can therefore not serve to accurately assess the proportion of eligible patients for BLVR in the total population of patients with emphysema. Secondly, inherent to the retrospective nature of this study, we had to rely on the quality of the referral documentation from other hospitals. Incomplete or incorrect referral documentation might have especially affected the data presented on comorbidity, which was based on the medical history included in the referral documentation, probably leading to an underestimation of comorbidity (31). Thirdly, the CT scans were of very different quality and settings, because referral material was used, making a preferred quantitative assessment not possible (34). These scans were assessed by one reviewer only (JBAW), under supervision of one of the authors (DJS), a task that in an ideal setting would have been performed by a panel of reviewers. Fourthly, since these were the first 1500 BLVR referrals sent to our hospital, most patients were treated in a clinical trial context, which probably led to a more strict selection compared to treatment outside clinical trial context, underestimating the number of patients eligible for BLVR treatment. Fifthly, it would have been of additional value to include a survival prediction index like BODE, but we did not have the necessary data available to perform this (35).

A strength of our study is the large number of patients that were included in this retrospective study. Another strength of our study is the fact that we were able to verify the survival status of our patients with the Dutch government, which increased the reliability of our survival data.

Future research might include the development of a model that is able to predict the à priori chances of BLVR eligibility. Such a model could assist both physicians and patients in deciding whether referral to a BLVR centre is indicated. Indeed, the right patient should be referred for the right treatment, to improve efficiency and avoid the burden for the patient. Future research is needed to identify the size of the potential pool of patients eligible for BLVR treatment as a previous study by Pietzsch et al suggested that BLVR currently is only used in a small proportion of patients with severe emphysema (36).

In conclusion, we found that only a small proportion of patients that are referred for BLVR treatment is eligible for a BLVR treatment, indicating a need for the development of new therapies for this group of patients and better referral tools. Furthermore, our data suggest that selection for BLVR is associated with a significant survival benefit.

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CHAPTER 4

Significant differences in body plethysmography measurements between hospitals in patients referred for bronchoscopic lung volume reduction

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ABSTRACT

Background: During the evaluation of potential bronchoscopic lung volume reduction (BLVR) candidates in our hospital, we frequently observe patients with a lower residual volume (RV) value compared to the value measured in their referring hospital, although both measured by body plethysmography. We explored to what degree RV and other pulmonary function measurements match between referring hospitals and our hospital.

Methods & Results: We retrospectively analysed a total of 300 patients with severe emphysema (38% male, median age 62 years (range 38-81), median forced expiratory volume in 1 second 29% (range 14-65) of predicted and a median of 40 packyears (range 2-125)). We measured a median RV of 4.47 liter (range 1.70-7.57), which was a median 310ml lower than in the referring hospitals (range -3.04 - +1.94), $P<0.001$).

Conclusions: In conclusion, this retrospective analysis demonstrated differences in RV measurements between different hospitals in patients with severe emphysema. Overestimation of RV can lead to unnecessary referrals for BLVR and potential treatment failures. To avoid disappointment and unnecessary hospital visits, it is important that body plethysmography measurements are accurately performed by applying preferably the unlinked method in these patients.

INTRODUCTION

Bronchoscopic lung volume reduction (BLVR) is a valid treatment option for selected patients with severe emphysema (1,2). Besides having significant emphysema, the key selection criterion for this treatment is the presence of severe static lung hyperinflation, defined as residual volume (RV) of >175% of the predicted value (3). Measuring RV can be performed using body plethysmography, helium gas dilution, nitrogen washout and quantification of lung volumes on a thoracic CT scan, but all can be technically challenging (4). In patients with severe emphysema, body plethysmography is the preferred method to measure RV, as gas dilution techniques tend to underestimate lung volumes in patients with obstructive lung disease and as CT scan imaging needs full expiration, which is difficult to accurately monitor in the radiology lab (5).

During the evaluation of potential BLVR candidates in our hospital, a BLVR expert center, we frequently observe patients with a lower RV value compared to the value measured in their referring hospital, although both measured by body plethysmography. When the RV value is too low for BLVR treatment, this may lead to disappointment of patients and their caregivers, together with unnecessary, time-consuming and expensive hospital visits, and even wrong treatment selection. We therefore explored to what degree RV and other pulmonary function measurements match between referring hospitals and our hospital, where we strictly adhere to the published guidelines.

METHODS

Using a retrospective analysis we included patients with severe emphysema who were referred from 62 different hospitals in the Netherlands to our hospital for BLVR evaluation between June 2012 and September 2017. Patients who had both body plethysmography and spirometry measurements available in their referring hospital as well as in our hospital, within an interval of less than one year between these measurements were included. In our hospital, spirometry and body plethysmography (MasterScreen™, Vyaire Medical, Mettawa, USA) were performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) standards (4,6). The equipment and guidelines used in the referring hospitals were unknown. Data is presented as median (range). Differences in lung function outcomes between referring hospitals and our hospital was analyzed with a Wilcoxon Signed Rank test. The association between differences in RV and time between measurements in

referring hospitals and our hospital was assessed using Spearman's rho. This analysis was part of a study which was approved by our local medical ethics committee. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

A total of 300 patients with severe emphysema (38% male, median age 62 years (range 38-81), median forced expiratory volume in 1 second (FEV_1) 29% (range 14-65) of predicted and a median of 40 packyears (range 2-125)) were included.

We measured a median RV of 4.47 liter (range 1.70-7.57), which was a median 310ml lower than in the referring hospitals (range -3.04 - +1.94), P<0.001). Furthermore, we observed significantly higher vital capacity (VC), lower total lung capacity (TLC) and lower intrathoracic gas volume (ITGV) than the referring hospitals (table 1).

Median time between RV measurements was 118 days (23-364). There was no correlation between differences in RV and time between both measurements (Spearman's rho=0.06, P=0.29).

Of the patients with an RV higher than 175% of predicted in their referring hospital, 34 patients (11%) were not accepted for BLVR treatment due to an RV less than 175% of predicted when re-measured in our hospital. In addition, 133 out of 300 (44%) patients had a larger difference in RV between hospitals than the established minimal important difference (MID) (>400ml decrease) (7). In comparison, 30 out of 300 (10%) patients had a lower RV in the referring hospital, compared to our hospital that was larger than the MID.

A selection of patients (n=82) underwent a second body plethysmography measurement in our hospital within one year (often for clinical trial purposes), with a median time between measurements of 69 days (7-352). There was no significant difference between the two RV measurements within our hospital (median difference 0.07 liter (P=0.43)).

Table 1: Pulmonary function outcomes

	N	Referring Hospitals	Our hospital	Median Difference	P-Value
RV (liter)	300	4.84 (1.75-9.89)	4.47 (1.70-7.57)	0.31 (-3.04-1.94)	P<0.001
RV%pred (%)	299	224 (98-392)	212 (107-350)	15 (-119-171)	P<0.001
TLC (liter)	297	7.58 (4.19-12.7)	7.47 (4.21-12.1)	0.11 (-2.63-4.69)	P<0.001
RV/TLC (ratio)	297	0.63 (0.40-0.87)	0.59 (0.34-0.80)	0.04 (-0.34-0.14)	P<0.001
VC (liter)	281	2.75 (1.11-6.46)	3.02 (1.46-6.77)	0.20 (-1.18-3.65)	P<0.001
ITGV (liter)	257	5.71 (1.74-11.0)	5.63 (2.41-10.2)	0.07 (-3.11-3.03)	P=0.01
FEV_1 (liter)	298	0.81(0.34-2.17)	0.82 (0.35-2.50)	0.01 (-0.64-1.25)	P=0.10
FEV_1%pred (%)	298	29 (14-65)	31 (15-73)	0.87 (-17-35)	P<0.01

Data are presented as median (range). N: number of patients; RV: residual volume; %pred: percentage of predicted; VC: vital capacity; TLC: total lung capacity; ITGV: intra thoracic gas volume; FEV_1: forced expiratory volume in 1 second. Differences between referring hospitals and our hospital was analyzed with a Wilcoxon Signed Rank test.

DISCUSSION

Eleven percent of patients who were referred for treatment were directly excluded from BLVR treatment because of lower RV outcomes in our hospital. Our findings are in line with previous research performed in children by Paton *et al.*, who compared spirometry and plethysmography outcomes between different hospitals and also found significant differences in RV and TLC even after standardization of procedures and equipment between hospitals without finding a significant difference in spirometry outcomes (8).

There are several possible explanations for the between hospital differences in RV. Different body plethysmography measurement techniques could have been applied. This is supported by statistically significant differences in both VC as well as ITGV outcomes between our hospital and the referral hospitals. Different approaches could be the use of linked versus unlinked VC manoeuvres (9). Potentially, time between measurements and thus progression of disease could have led to the difference between RV outcomes, but this would result in an increase of RV instead of a decrease. We did not find a significant association between time between measurements and RV. A selection of patients (n=82) underwent a second body plethysmography measurement in our hospital just before BLVR treatment. There was no significant difference in absolute RV outcome within an interval of 1 year, suggesting RV measurement consistency in our hospital.

We applied an RV 175% of predicted threshold for BLVR eligibility, which was based on the 2019 BLVR expert panel recommendations and in line with the latest published clinical trial investigating EBV treatment (LIBERATE)(10,11).

This study has several limitations. First, an arbitrary maximum interval of 1 year between two plethysmography measurements was used, however when using a 6 months interval, absolute RV between hospitals was still significantly different ($P<0.001$, $n=222$). Secondly, we were not aware of patient conditions when they performed the measurement in their referring hospital, which could have influenced RV outcomes. Possibly, body plethysmography measurements in referring hospitals were performed during exacerbations of disease, leading to higher RV outcomes in the referring hospitals (12,13). Thirdly, we could not verify that all body plethysmography measurements in the referring hospitals were performed after bronchodilator administration and we were unaware of the guidelines and equipment used. Fourthly, even though the application of the unlinked method probably resulted in lower RV outcomes in our hospital, compared to the referring hospitals, we did not have data available supporting improved patient outcomes after BLVR as a consequence of this technique.

Based on our clinical experience, we have the following suggestions to reduce overestimation of RV in severe emphysema patients during body plethysmography measurement. First, the pulmonary function technician who performs the measurement should take a considerate amount of time to ensure that patients achieve a full expiration state when performing the ERV manoeuvre during the inspiratory VC measurement. Secondly, the presence of dynamic hyperinflation should be prevented by reducing physical effort just before measurement as well as allowing the patient to get off the mouthpiece between manoeuvres (14). Thirdly, we suggest the use of the unlinked manoeuver. This means that directly after the ITGV manoeuver, the IC measurement will be performed and that the maximum VC measured during spirometry is used for the calculation of RV. Particularly for patients with severe emphysema, it is difficult to perform a maximal VC manoeuver directly after the ITGV manoeuver, resulting in an underestimation of VC and therefore an overestimation of RV. Finally, we suggest that the measurement is performed in a stable state after optimal bronchodilation.

The estimation of lung volumes using quantitative CT analysis could become a valuable tool in the future (15). However this method relies heavily on both the

quality of the analyzed scans as well as reaching a full in- and expiration state during scanning.

In conclusion, this retrospective analysis demonstrated differences in RV measurements between different hospitals in patients with severe emphysema. Overestimation of RV can lead to unnecessary referrals for BLVR and potential treatment failures. To avoid disappointment and unnecessary hospital visits, it is important that body plethysmography measurements are accurately performed by applying preferably the unlinked method in these patients.

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CHAPTER 5

A new oxygen uptake measurement supporting target selection for endobronchial valve treatment

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ABSTRACT

Background: Adequate target lobe selection for endobronchial valve (EBV) treatment in patients with severe emphysema is essential for treatment success and can be based on emphysema destruction, lobar perfusion, lobar volume and collateral ventilation. As some patients have more than one target lobe for EBV treatment we were interested whether we could identify the least functional lobe.

Objective: The objective of this study was to investigate the relationship between endoscopic lobar measurement of oxygen uptake, lobar destruction and vascular volume and whether this could help in identifying the least functional lobe and thus optimal target for EBV treatment.

Methods: We prospectively included patients who were scheduled for EBV treatment in our hospital. A customized gas analysis set-up was used to measure lobar O_2 uptake after lobar balloon occlusion. Quantitative CT analysis was performed to assess degree of emphysematous destruction and lobar arterial and venous volumes.

Results: Twenty-one (5 male/16 female) patients with emphysema (median age 63 years, FEV_1 25% of predicted, residual volume 234% of predicted) were included and 49 endoscopic lobar measurements were performed. A lower O_2 uptake significantly correlated with a higher degree of emphysematous lobar destruction (Spearman's rho: 0.39, $P<0.01$), and with a lower arterial and venous vascular volumes of the lobes (respectively -0.46 and -0.47, both $P<0.001$).

Conclusions: Endoscopic measurement of lobar O_2 uptake is feasible in patients with emphysema. Measurement of lobar O_2 uptake helped to identify the least functional lobe and can be used as additional tool for EBV target lobe selection.

INTRODUCTION

Endobronchial valve (EBV) treatment is a minor invasive and effective bronchoscopic lung volume reduction treatment in selected patients with severe emphysema (1–4). The purpose of EBV treatment is to induce lobar atelectasis by occluding all segmental bronchi of a destructed and hyperinflated lobe with one-way valves (5). Patient selection is essential for EBV treatment success and important selection criteria are the presence of a suitable emphysematous target lobe with absence of collateral ventilation (CV), the degree of lung hyperinflation and absence of significant comorbidity (5). Target lobe selection is based on the degree of emphysema destruction, absence of collateral ventilation (CV), lobar volume of the target lobe and ipsilateral lobe, low lobar perfusion assessed using perfusion scintigraphy and absence of pleural adhesions (6–8).

Some patients have more than one suitable target lobe for EBV treatment. Quantitative CT analysis may help to identify the most suitable target lobe for treatment. In addition to quantitative CT analysis, perfusion scintigraphy may also help to identify the target lobe in these patients, preferably targeting the lobe with the lowest perfusion (9). However, in our hospital we encounter patients who after applying all available diagnostic techniques, still have more than one target lobe eligible for EBV treatment.

Freitag *et al.* previously demonstrated the use of endoscopic capnometry and oximetry curves to improve EBV target zone identification (10). Building on this approach, we wanted to investigate whether the quantification of lobar oxygen (O_2) uptake capacity might help identifying the least functional lobe, and therefore best target lobe for EBV treatment.

The objective of this study was to investigate the relationship between endoscopic lobar measurement of oxygen uptake, lobar destruction and vascular volume and whether this could help in identifying the least functional lobe and thus optimal target for EBV treatment.

METHODS

Study design

In this prospective feasibility study we included patients with severe emphysema who were scheduled for EBV treatment in a national treatment registry (BREATH-NL: NCT02815683), in our hospital from February 2018 to May 2018. All patients provided written informed consent for the treatment procedure, flow measurements, and data collection.

Outcomes

The primary outcome of this study was the association between the degree of lobar emphysematous destruction and O_2 uptake capacity.

Secondary, we wanted to investigate the association of the uptake capacity of O_2 in the measured lobes with the vascular quantitative CT (QCT) parameters: arterial and venous volumes of the lobes. Furthermore, the association between lobar emphysematous destruction and arterial and venous volume of the lobes was assessed.

Equipment

Endoscopic O_2 concentration measurements were performed using a customized set up. An ISA® sidestream gas analyser (Masimo AB, Danderyd, Sweden) was used, sampling air at 50ml per minute and collecting data 20 times per second (10). To achieve lobar isolation, a Chartis® catheter (Pulmonx Inc., Redwood City, CA, USA) was used. The Chartis catheter is equipped with an inflatable balloon tip and can be advanced through the working channel of a flexible bronchoscope (6). A Nomoline® sampling line (200cm) (Masimo AB) was used to prevent moisture from disturbing the gas measurements. The sampling delay caused by the length of the Chartis catheter and Nomoline was approximately 2 seconds. A Tangent® console (Burlingame, USA) running customized software (Pulmonx Inc. Redwood City, CA, USA) was used to allow characterization and live visualization of data during the measurements, as well as data extraction after the procedure. An overview of the measurement set up can be found in figure 1.

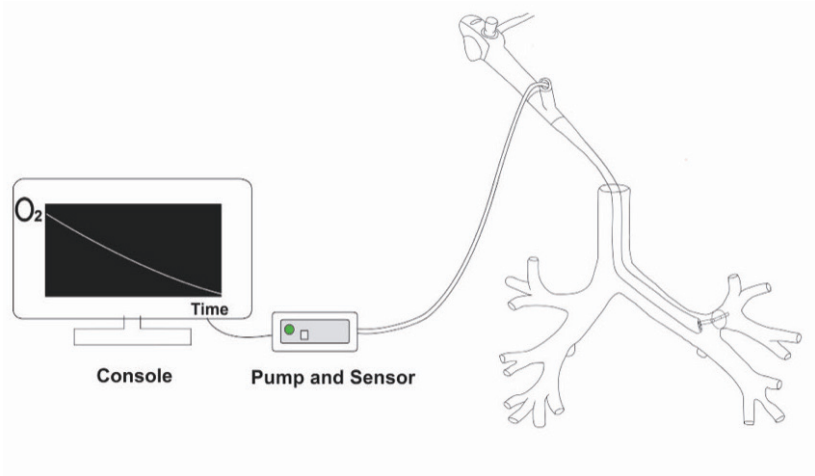

Figure 1: Schematic representation of the measurement set-up demonstrating occlusion of the left upper lobe.

Measurement

The presence of interlobar collateral ventilation was assessed in every patient using the Chartis measurement. After the Chartis measurement, the entrance of the lobe selected for measurement was occluded by inflating the balloon of the Chartis catheter again, effectively isolating this lobe for 2 minutes. Directly after occlusion the O_2 uptake measurement was started by measuring the oxygen concentration distal of the inflated balloon. Measurements were performed in at least the EBV treatment target lobe as well as the adjacent lobe. The right middle lobe was excluded from measurement.

Measurements were only included for analysis when absence of CV was confirmed by Chartis and a reliable gas concentration signal was obtained. Measurements were excluded from analysis when total airway collapse occurred, when mucus occluded the catheter distorting the measurements or when the balloon occlusion of the airway was lost during measurement.

Measurements (as well as Chartis and the EBV procedure) were performed under general anesthesia. Patients were intubated with a flexible 9 mm endotracheal tube. The primary ventilator settings were: volume controlled ventilation mode with target settings of low ventilation frequency (8–10 times per minute), tidal volumes 4-6ml/kg, fixed fraction of inspired oxygen (FiO_2) of 50%, long expiratory settings (inspiratory/expiratory ratio of 1:3 to 1:4) and positive end-expiratory pressure of 3 cm H_2O.

Quantitative CT Analysis

Lobar emphysematous destruction and lobar volumes were determined using the StratX® QCT platform (Pulmonx, Inc, Redwood City, CA, USA). The assessment of arterial and venous volume per lobe was performed using Thirona Lung Quantification software® (Thirona, Nijmegen, Netherlands) (see figure 2).

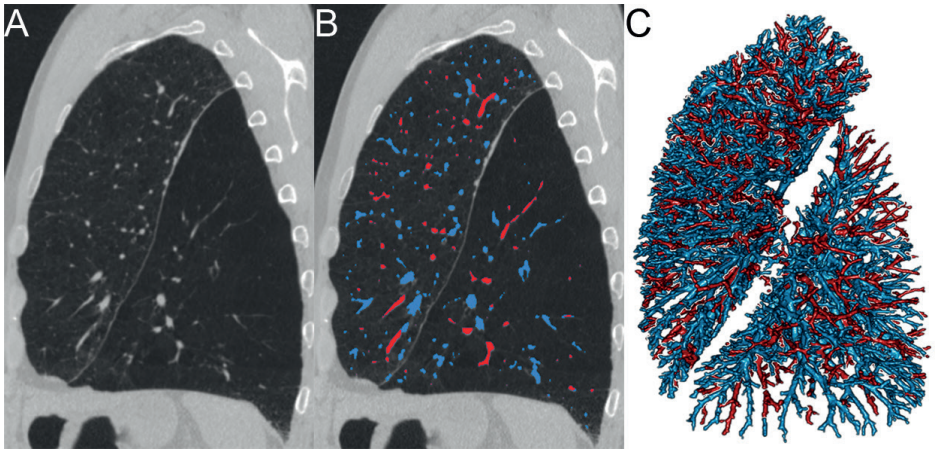

Figure 2: Quantitative CT analysis of arterial and venous volume. Plot A: Sagittal view of the left lung with left lower lobe predominant emphysema. Plot B: 2D artery-vein overlay of the left lung with decreased vascular volume in the left lower lobe. Plot C: 3D artery-vein rendering of the left lung.

Statistical analysis

Linear regression was performed to quantify O_2 uptake capacity with O_2 concentration as a dependent variable and measurement duration as independent variable. Slope coefficients were derived of O_2 uptake capacity (change in $\%O_2$ per second) for each measurement.

Spearman's rho was used to test the association between O_2 uptake capacity and lobar emphysematous destruction (percentage of voxels less than -950 Hounsfield units), the association between O_2 uptake capacity and arterial or venous volume in the measured lobes, the association between arterial and venous volume and lobar emphysematous destruction and the association between O_2 uptake capacity and lobar volume. P-values <0.05 were considered significant. Statistical analyses were performed using SPSS version 23 (IBM, New York, NY, USA).

RESULTS

Patients

Twenty-one patients were included with a median age of 63 years (range 39-73), 24% male and a forced expiratory volume in one second (FEV_1) of 25% of predicted (range 13-39). Patient characteristics can be found in table 1.

Table 1: Patient Characteristics

Characteristics	
n	21
Female/Male (%)	76/24
Age (years)	63 (39-73)
BMI (kg/m^2)	23 (19-35)
Pack-years (years)	40 (9-147)
FEV_1%predicted (%)	25 (13-39)
RV%predicted (%)	234 (175-327)
TLC%predicted (%)	141 (111-170)
RV/TLC (ratio)	0.7 (0.5-0.8)
DLCO (mmol/minute*kPa)	2.0 (1.4-4.0)
DLCO%predicted (%)	27 (19-40)
6MWD (meter)	287 (111-479)
SGRQ total score (units)	61 (40-82)

Data is presented as median(range). N: number of patients; BMI: Body mass index; FEV_1: forced expiratory volume in 1 second; RV: Residual volume; TLC: Total lung capacity; DLCO: diffusion capacity for carbon dioxide; 6MWD: 6-minute walking distance; SGRQ: St. George's Respiratory Questionnaire.

O_2 uptake measurements

We performed O_2 uptake measurements in 69 different lobes and of these we included 49 in our analysis, see table 2. Measurements were performed in the right upper lobe (n=9), right lower lobe (n=7), left upper lobe (n=17) and the left lower lobe (n=16). Twenty of 69 measurements (29%) were excluded from analyses because of the following reasons: interlobar CV was present (n=8), no full airway seal was achieved with the balloon or this seal was lost during measurement (n=5), severe airway collapse occurred (n=3), no flow state was encountered (n=1) and unspecified measurement failure (n=3).

Table 2: Gas and quantitative CT measurements

Variables	
Number of measurements	49
Oxygen uptake (%O_2/second)	-0.11 (-0.31- -0.01)
Duration of measurement (seconds)	124 (63-304)
Emphysematous destruction in measured lobe (%voxels <-950HU)	40 (5-60)
Lobar volume (ml)	1574 (912-3009)
Lobar vascular volume (ml)	101 (59-165)
Lobar arterial volume (%)	3.9 (2.5-6.0)
Lobar venous volume (%)	2.6 (1.5-4.0)

Data are presented as median (range). HU: Hounsfield units.

The average O_2 uptake was 0.13±0.06% O_2 decrease per second, indicating an average decrease of 50% $Fi0_2$ to 34.4% during a two minute measurement.

A higher degree of lobar emphysematous destruction was significantly associated with a lower O_2 uptake (Spearman's rho: 0.39, P<0.01). Furthermore, a lower arterial and venous volume on QCT of the measured lobes was significantly correlated with lower O_2 uptake (respectively rho: -0.46 and -0.47, both P<0.001). Lower arterial and venous volume of the lobes were significantly associated with higher lobar emphysematous destruction (both rho -0.60, P<0.001). No significant association was found between lobar volume and O_2 uptake capacity (rho: -0.13, P=0.37). Scatterplots can be found in figure 3.

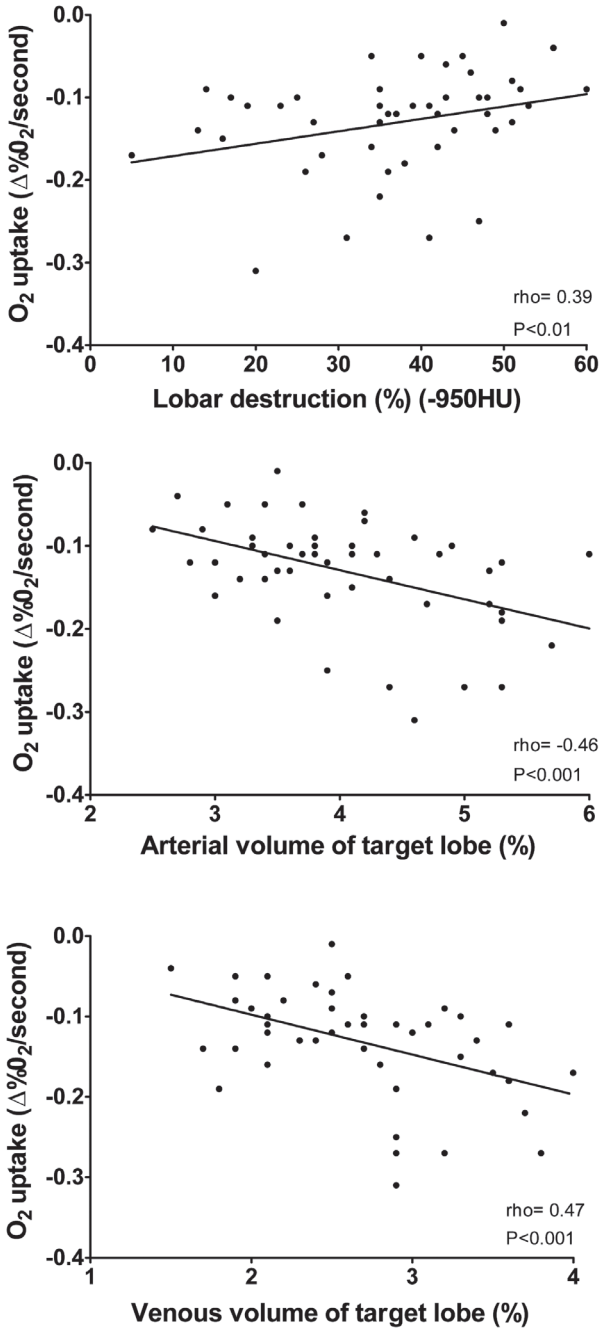

Figure 3: Scatterplots of oxygen uptake capacity versus lobar destruction, arterial and venous volume of the target lobes.

DISCUSSION

In this study we investigated a functional endoscopic approach to EBV target lobe selection: selective lobar measurement of O_2 uptake capacity. A lower O_2 uptake was significantly correlated with higher lobar emphysematous destruction and lower arterial and venous vascular volume of the target lobes.

To our knowledge, this is the first study describing endoscopic lobar O_2 uptake measurement to improve EBV target selection in patients with severe emphysema. Freitag *et al.* previously demonstrated target zone identification guided by endoscopic capnometry and oximetry curves using a similar measurement set-up, and were able to improve target zone identification using this technique, but this approach did not allow for quantification of lobar uptake capacity (10). Adequate target lobe selection for EBV treatment is critical since complete occlusion of a lobe with a relatively high uptake capacity for O_2 can lead to respiratory insufficiency, instead of the patient benefitting from the treatment.

Oxygen uptake in a lobe can be influenced by several factors. First of all, oxygen uptake is dependent on the amount of local perfusion. In this study, QCT analysis was performed to assess arterial and venous volume in the target lobes, serving as a surrogate measure of local perfusion. In future studies, the comparison of Single Photon Emission Computed Tomography outcomes to endoscopic lobar O_2 uptake capacity could be of additional value. Secondly, O_2 uptake capacity depends on the integrity of local lung tissue and alveoli in the target lobes, which is why we related our endoscopic O_2 uptake measurements to QCT analysis of emphysematous destruction in this study. A third factor that could influence local O_2 uptake is variance in cardiac output, which in our study was not assessed during the procedure (11). A fourth factor is the time between deflation of the Chartis balloon after collateral ventilation measurement and the re-inflation of this balloon for oxygen uptake measurement. Considering the minimum amount of one minute needed to convert to oxygen uptake measurement after CV measurement, our ventilation settings and knowing that a median 390ml of air is expired during Chartis measurement in CV negative lobes, we do not believe that this factor played a significant role in this study (12). A last factor is the alveolar-arterial pressure gradient of oxygen, which depends on the FiO_2 (11). For standardization reasons we ventilated all our patients with an FiO_2 of 50%, using the same ventilator settings, avoiding high peak pressures of ventilation.

This study has several limitations. All measurements were performed while patients were on positive pressure ventilation during general anesthesia, which could have affected measurement outcomes when compared to spontaneously breathing patients, however in clinical practice it is recommended to perform both the Chartis measurement as well as the EBV procedure under general anesthesia (12). In all patients a supranormal standardized F_IO_2 of 50% was maintained during the procedure, in order to magnify the O_2 slope signal. The measurements were performed during an arbitrary two minutes interval, and to assess O_2 uptake, linear regression was performed to calculate slope coefficients. Possibly, with extension of measurement, the O_2 uptake pattern that now exhibited linear relationship properties would have exhibited exponential function properties. Our measurement set up had a measurement delay of 2 seconds due to catheter length, perhaps in future research other measurement techniques such optical fiber probes could be used to achieve gas concentration measurements with less delay (13).

Lobes that were diagnosed as CV positive by Chartis measurement were excluded from our analysis as the supply of oxygen through interlobar collateral channels could disturb oxygen uptake measurements in the isolated lobes. One might even elaborate on the possibility of this being an alternative to the current measurement of CV using flow instead of gas components.

In our experience, the measurements were feasible, easy to perform and provided insight that was of additional value in target lobe selection for EBV treatment. Future developments in this field could include the development of a console displaying live O_2 consumption rate during bronchoscopy.

In conclusion, endoscopic measurement of lobar O_2 uptake is feasible in patients with emphysema. This new functional endoscopic approach to measure O_2 uptake capacity at a lobar level can prove an additional diagnostic tool to improve identification of a treatment target for lung volume reduction treatment with endobronchial valves, however more research is needed to validate this approach.

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CHAPTER 6

Chartis measurement of collateral ventilation: conscious sedation versus general anesthesia; a retrospective comparison

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ABSTRACT

Background: Absence of interlobar collateral ventilation using the Chartis measurement is the key predictor for successfull endobronchial valve treatment in severe emphysema. Chartis was originally validated in spontaneous breathing patients under conscious sedation (CS), however this can be challenging due to cough, mucus secretion, mucosal swelling and bronchoconstriction. Performing Chartis under general anesthesia (GA) avoids these problems and may result in an easier procedure with a higher succes rate. However, using Chartis under GA with positive pressure ventilation has not been validated.

Objectives: In this study we investigated the impact of anesthesia technique, CS versus GA, on the feasibility and outcomes of Chartis measurement.

Methods: We retrospectively analyzed all Chartis measurements performed in our hospital from October 2010 until December 2017.

Results: We analyzed 250 emphysema patients (median FEV_1 26% (range 12%-52%predicted). In 121 patients (48%) the measurement was performed using CS, in 124 (50%) using GA and in 5 (2%) both anesthesia techniques were used. In total 746 Chartis readings were analyzed (432 CS, 277 GA and 37 combination). Testing under CS took significantly longer than GA (median 19 minutes (range 5-65) versus 11(3-35), P<0.001) and required more measurements (3(1-13) versus 2(1-6), P<0.001). There was no significant difference in target lobe volume reduction after treatment (-1123(-3604-332)ml) in CS versus -1251(-3333--1) in GA, P=0.35.

Conclusions: In conclusion, Chartis measurement under CS took significantly longer and required more measurements than under GA, without a difference in treatment outcome. We recommend a prospective trial comparing both techniques within the same patients to validate this approach.

INTRODUCTION

Bronchoscopic lung volume reduction using endobronchial one-way valves (EBV) has been shown to be clinically effective, and to have an acceptable safety profile in selected patients with severe emphysema (1–5). Maximal clinical improvement after endobronchial valve treatment is associated with complete lobar atelectasis (1,2,6–8). However, lobar atelectasis will not be achieved in the presence of interlobar collateral ventilation due to an incomplete interlobar fissure. In approximately 60% of the patients with severe emphysema the interlobar fissure is not complete (9). Interlobar collateral ventilation can be measured using the Chartis System® (Pulmonx Inc., Redwood City, CA, USA).

The Chartis system was originally validated in patients using conscious sedation (8,10). However, in clinical practice the Chartis measurement is also often performed using general anesthesia for practical reasons. Under conscious sedation, measurements are often challenging to perform or even fail, due to increased coughing, mucus secretion, bronchoconstriction, swelling of mucosa and difficulty to maintain an optimal level of sedation. Therefore, general anesthesia was recently suggested to be the preferred and recommended technique for both the Chartis measurement and the subsequent endobronchial valve placement due to the ease of airway and patient management (11).

To our knowledge, effects of conscious sedation and general anesthesia on the Chartis measurement have never been compared in the literature. The objective of this study was to investigate the impact of anesthesia technique, conscious sedation versus general anesthesia, on both feasibility of the Chartis measurement and the outcome of subsequent endobronchial valve placement.

METHODS

Study design and population

Retrospectively, we analyzed data of all patients who underwent a Chartis measurement in our University Medical Center Groningen, the Netherlands. From October 2010 until December 2017, we performed Chartis measurements in 250 patients in different trials ("CHARTIS trial" (8), "STELVIO trial" (1), "IMPACT trial" (4), "TRANSFORM trial" (5), "BREATH-NL registry" (NCT02815683) and in patients treated in a compassionate use setting (Table 1). All trials had prior approval from the local ethics committee and all patients provided informed consent.

Table 1: Patients per anesthesia technique per study

	Conscious Sedation	General Anesthesia	Combination
CHARTIS (2013) [8]	29 (24%)	1 (1%)	0
STELVIO (2015) [1]	80 (66%)	0 (0%)	4 (80%)
IMPACT (2016) [4]	5 (4%)	20 (16%)	1 (20%)
TRANSFORM (2017) [5]	0 (0%)	15 (12%)	0
BREATH-NL	0 (0%)	75 (60%)	0
Compassionate use	7 (6%)	13 (11%)	0
Total	121 (100%)	124 (100%)	5 (100%)

Data is presented as number of cases (percentage of total cases).

Anesthesia technique

Conscious sedation is a drug-induced state of reduced consciousness during which patients are able to purposefully respond to verbal commands or light tactile stimuli and are able to maintain oxygenation and airway control without intervention (12). Conscious sedation was induced with intravenous propofol and remifentanil. Medication dosage was titrated up to a level where patients were adequately sedated but still arousable and breathing spontaneously. In addition a 1% w/v lidocaine spray was applied locally to the upper and lower airways.

General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation, spontaneous ventilation cannot be maintained and an artificial maintenance of open airway is necessary (12). General anesthesia was induced through administration of intravenous propofol and remifentanil and muscle relaxation was achieved with rocuronium bromide. Patients were intubated with a flexible 9 mm endotracheal tube and positive pressure ventilation was applied with target settings of low ventilation frequency (8-10x/minute), long expiratory settings (inspiratory/expiratory ratio of 1:3) and positive end-expiratory pressure of 3cm H_20 (11).

Chartis measurement

Collateral ventilation measurements were performed using the Chartis System® (Pulmonx Inc., Redwood City, CA, USA). The Chartis system consists of a catheter, with an inflatable balloon at the tip, which can be advanced through the 2.8 mm or larger working channel of a bronchoscope (figure 1). Inflation of the balloon allows for temporary occlusion of the airway, during which airflow coming from the occluded lobe can be assessed (13). Expired airflow volume, pressure and resistance

measurements are analyzed and visualized by the Chartis console. Distinctive airflow patterns allow for assessment of collateral ventilation status (figure 2) (9).

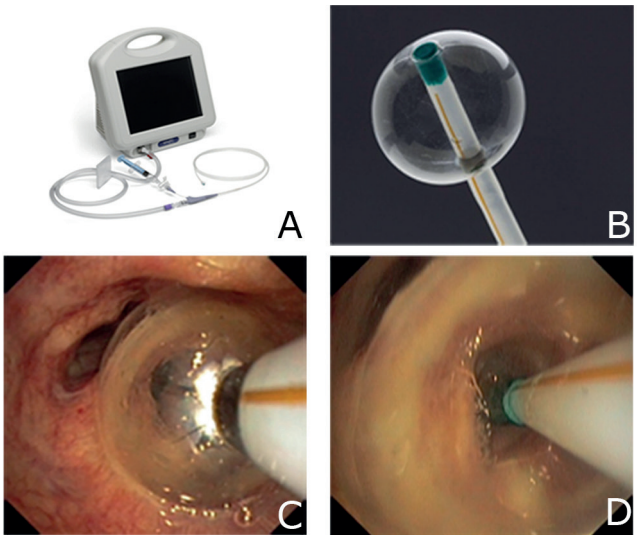

Figure 1: Chartis system® (Pulmonx Inc., Redwood City, CA, USA). Console with catheter (Panel A). Catheter with inflated balloon at tip (Panel B). Bronchoscopic view of inflated balloon at catheter tip in airway (Panel C). Bronchoscopic view through inflated balloon at catheter tip in airway (Panel D).

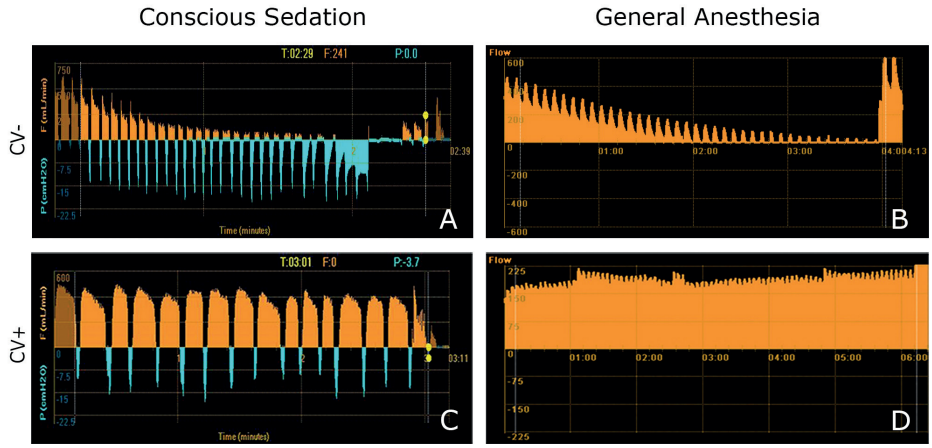

Figure 2: Chartis measurement reports for the 4 different categories: Negative collateral ventilation under conscious sedation (Panel A), negative collateral ventilation under general anesthesia (Panel B), positive collateral ventilation under conscious sedation (Panel C) and positive collateral ventilation under general anesthesia (Panel D).

Outcome variables

We analyzed the Chartis measurements that were performed in the pre-determined treatment target- and ipsilateral lobes.

Our primary outcome was the total duration of Chartis measurement, defined as the total duration of all measurement attempts combined. Secondary outcomes were the number of Chartis measurements performed per patient, number of measurements per lobe, amount of lobes measured, expired airflow volume measured with Chartis, target lobe volume reduction (TLVR) after treatment, and Chartis outcome category. The Chartis outcome was categorized by the treating physician in 4 different categories: 1) negative collateral ventilation 2) positive collateral ventilation 3) undetermined measurement (signal output but not possible to determine collateral ventilation status, caused by for example touching of the bronchial wall by the Chartis catheter tip, secretion occlusion of the catheter leading to low/no flow or measurement distortion by coughing and patient exhaling during exertion) and 4) discarded measurement (not possible to obtain valid signal output due to loss of balloon seal and total catheter blockage due to excessive mucus).

TLVR was calculated using different quantitative high resolution computed tomography software per study protocol. Scans were analyzed using Thirona LungQ (Nijmegen, The Netherlands) (STELVIO, BREATH-NL registry and compassionate use), VIDA Diagnostics software (Coralville, IA, USA) (TRANSFORM and IMPACT) or MedQia software (Los Angeles, CA, USA) (CHARTIS).

Statistical analysis

To compare differences in patient characteristics, measurements duration, number of Chartis measurements, number of measurements per lobe, amount of lobes measured, expired airflow volume and TLVR between conscious sedation and general anesthesia, an Independent-Samples T-test was performed in case of normal distribution of data and a Mann-Whitney-U test in case of non-normal distribution. P-values below 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22 (IBM, New York, NY, USA).

RESULTS

Of the 250 included patients, 121 (48%) patients underwent conscious sedation and 124 (50%) patients underwent general anesthesia. Five patients (2%) received both anesthesia techniques after conversion from conscious sedation to general anesthesia; these were not used in the analyses (see figure 3 for patient flowchart, patient characteristics are shown in table 2). No direct anesthesia related complications were observed in either groups.

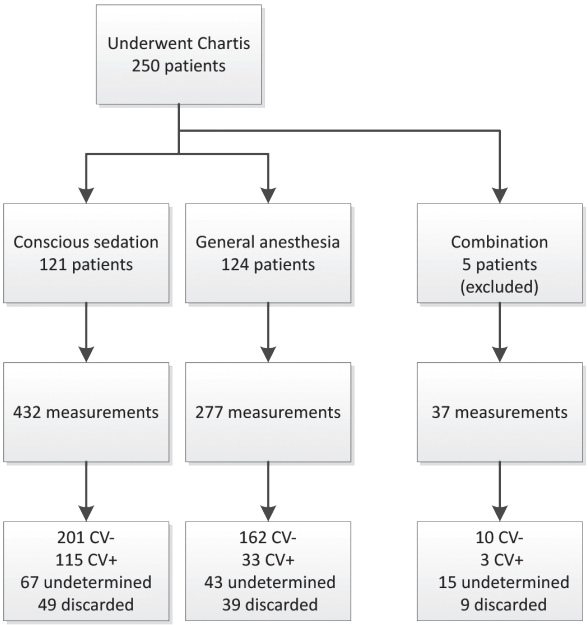

Figure 3: Patient flowchart. Patients who received both conscious sedation and general anesthesia were not included in the analysis. CV-: negative collateral ventilation; CV+: positive collateral ventilation.

The Chartis measurement outcomes per anesthesia technique are provided in table 3. Chartis measurement under conscious sedation took significantly (P<0.001) longer than under general anesthesia (median 19 minutes (range 5-65) versus 11 (3-35)), required a significantly (P<0.001) higher number of measurements (3 (1-13) versus 2 (1-6) and required a significantly (P<0.001) higher number of measurements per lobe (2(1-7) versus 1 (1-3). The proportions of undetermined and discarded measurements and the amount of lobes measured per patient were not significantly different between the groups (P>0.05).

Table 2: Patient characteristics

Characteristics	Conscious Sedation	General Anesthesia	Combination
n	121	124	5
Female/Male (%)	60/40	68/32	80/20
Age (years)	60 (36-78)	62 (42-78)	54 (47-68)
BMI (kg/m^2)	23.8 (17-37)	23.2 (16-35)	22.6 (20-26)
Pack-years (years)*	35 (0-110)	39 (8-148)	35 (18-60)
FEV_1%predicted (%)*	27.0 (12-52)	25.8 (12-48)	26.0 (23-32)
RV%predicted (%)*	216.0 (120-361)	232.5 (130-484)	245.0 (182-263)
6MWD (meter)*	361.3±95.4	316.6±100.3	411.8±72.7
SGRQ total score (units)	60.3±12.8	60.0±11.3	56.1±8.1
Target lobe volume (ml)	1747 (780-4666)	1632 (956-3755)	2146 (1067-2746)

Data is presented as mean ± standard deviation in case of normal distribution of data and as median(range) in case of non-normal distribution. BMI: Body mass index; FEV_1: forced expiratory volume in 1 second; RV: Residual Volume; 6MWD: 6-minute walking distance; SGRQ: St. George's Respiratory Questionnaire. Difference between conscious sedation and general anesthesia was analyzed with an Independent-Samples T-test in case of normal distribution of data and a Mann-Whitney-U test in case of non-normal distribution. *P<0.05 between conscious sedation and general anesthesia.

Median TLVR in the conscious sedation group was -1123(-3604-332)ml (relative TLVR 72%) compared to -1251(-3333--1)ml (relative TLVR 77%) in the general anesthesia group. Differences in both absolute as well as relative TLVR were not significant between anesthesia techniques.

In total 746 Chartis measurements (432 conscious sedation, 277 general anesthesia and 37 combination) were performed in the pre-determined target- or ipsilateral lobes, of which 373 were categorized as negative collateral ventilation, 151 positive collateral ventilation, 125 were undetermined and 97 were discarded measurements. Under conscious sedation the Chartis catheter balloon ruptured 3 times compared to once under general anesthesia.

In patients with absence of collateral ventilation, the expired airflow volume was significantly (P=0.015) higher under conscious sedation than under general anaesthesia (490ml (range: 6-2504) versus 390ml (range: 34-1561).

Table 3: Chartis measurement outcomes under conscious sedation and general anesthesia

	Conscious Sedation	General Anesthesia	Median Difference	P-Value
Measurement length				
Duration of total Chartis procedure per patient (seconds)	1140 (300-3900)	656 (180 -2100)	402	P<0.001
Sum of measurement duration per patient, excluding discarded measurements (seconds)	668 (103-2109)	398 (61-1211)	213	P<0.001
Sum of measurement duration per patient, in measurements with CV negative outcome (seconds)	356 (95-1469)	308 (65-875)	69	P=0.02
Amount of measurements				
Number of measurements per patient (number)	3 (1-13)	2 (1-6)	1	P<0.001
Number of measurements per patient, excluding discarded and undetermined measurements (number)	2 (0-13)	1 (0-4)	1	P<0.001
Number of discarded measurements (total amount in group (percentage of total measurements))	49 (11%)	39 (14%)	NA	P=0.97
Number of undetermined measurements (total amount in group (percentage of total measurements))	67 (16%)	43 (16%)	NA	P=0.22
Measurements per lobe, including discarded and undetermined measurements (number)	2 (1-7)	1 (1-3)	0.5	P<0.001
Measured lobes per patient, including discarded and undetermined measurements (number)	2 (1-4)	2 (1-4)	0	P=0.32
Analysed airflow volume				
Expired airflow volume per patient (ml)	903 (19-6719)	462 (34-7639)	333	P<0.001
Expired airflow volume per patient in measurements with CV negative outcome (ml)	(490 (6-2504)	390 (34-1561)	111	P=0.015
Target lobe volume reduction				
Target lobe volume reduction per patient (ml)	-1123 (-3604-332)	-1251 (-3333--1	112	P=0.35
Target lobe volume reduction per patient (%)	72 (100-24)	77 (100-0)	0	P=0.27

Data are presented as mean ± standard deviation in case of normal distribution of data and as median(range) in case of non-normal distribution. In case of categorical variables data is presented as n (%). Difference between conscious sedation and general anesthesia was analyzed with an Independent-Samples T-test in case of normal distribution of data and a Mann-Whitney-U test in case of non-normal distribution. CV: collateral ventilation.

DISCUSSION

To our knowledge, this is the first study comparing conscious sedation and general anesthesia during bronchoscopic evaluation of interlobar collateral ventilation with Chartis in patients with severe emphysema. The Chartis testing under conscious sedation took significantly longer and required a higher number of measurements in total and per lobe than general anesthesia, indicating the ease of use of Chartis under general anesthesia. In the EBV treated patients, after a CV negative Chartis measurement, no significant differences in TLVR were found between the conscious sedation and general anesthesia group, suggesting no inferiority of the diagnostic value of Chartis under general anesthesia.

The observed differences in duration and number of measurements could be the result of more frequent presence of mucus, coughing, bronchus constriction, airway wall edema and sedation problems, causing catheter obstruction in the conscious sedation group leading to more complex procedures and more difficult interpretation of Chartis results.

There are no studies reported that compared various techniques of anesthesia with respect to feasibility. A study by Gesierich *et al.*, compared airway collapse during Chartis measurement under spontaneous breathing and jet ventilation and recommended to use spontaneous breathing to prevent airway collapse (14).

In the patients who received general anesthesia in our study positive pressure ventilation via an endotracheal tube was applied.

Recently, a best practice recommendations panel on endoscopic lung volume reduction favored the use of general anesthesia for Chartis measurement and the subsequent endobronchial valve placement due to the ease of use, airway and patient management (11).

Five patients received both conscious sedation as well as general anesthesia. These patients were converted from conscious sedation to general anesthesia because the treating physician was unable to perform a valid measurement under conscious sedation, due to mucus presence, patient unrest, coughing and low flow. The fact that in some patients measurement was only possible in a general anesthesia setting might already indicate the better feasibility of this approach.

Arguments against the use of general anesthesia for Chartis measurement could be the higher dosage of medication received, compared to conscious sedation, as well as the intubation and ventilation of severe emphysema patients. Higher cost of the application of general anesthesia should be considered, especially in limited resource settings. On the other hand, the EBV procedure is much easier and faster to perform under general anesthesia. Furthermore, in our hospital patients are always scheduled for a combined Chartis measurement with a subsequent EBV procedure (and never for a diagnostic Chartis procedure alone to avoid an unnecessary additional bronchoscopy), making the use of general anesthesia for the Chartis procedure more practical. In addition, no anesthesia-related adverse events were reported in our patients. The use of both conscious sedation as well as general anesthesia is deemed safe in interventional pulmonology (15).

No significant differences in TLVR after treatment between the conscious sedation and general anesthesia group were found. This is an important finding since the Chartis measurement was not yet validated under general anesthesia. The absence of collateral ventilation in combination with successful EBV placement, resulting in sufficient target lobe volume reduction, is the driver for treatment success as TLVR is a predictor for clinically meaningful change after treatment (16,17).

A higher percentage of positive collateral ventilation measurements was found in the conscious sedation technique. One explanation could be the improved patient selection over time by quantitative high resolution computed tomography (fissure) analysis, which decreased the number of patients with positive collateral ventilation outcomes in Chartis measurement in the trials. In addition, the objective of the CHARTIS study, in which almost all patients underwent conscious sedation, was to determine whether Chartis assessment of collateral ventilation could predict significant TLVR after EBV placement, actively including patients with both negative as well as positive collateral ventilation status (8).

Baseline characteristics were significantly different for $FEV_{1,}$ RV and 6MWD, with the more severe patients being in the general anesthesia group. This difference can be explained by the fact that general anesthesia was more frequently applied in later trials which were open to inclusion of patients with more severe disease. We do not believe that the severity of emphysema influenced Chartis measurement outcomes, especially because (non-)intact fissures are probably not caused by emphysematous disease, but rather reflect an inherited trait (9).

The expired total airflow volume in patients with negative collateral ventilation was significantly higher under conscious sedation than under general anesthesia. This is an interesting finding, since we assumed that patients under conscious sedation with spontaneous breathing would rely on the elasticity of the lobe to exhale through the catheter, while patients under general anesthesia would have both elasticity as well as driving force from positive pressure in the adjacent lobe(s). Another possible explanation could be that due to an easier procedure under general anesthesia the sampling time was shorter leading to a lower amount of analysed airflow volume. The observed difference did not lead to a difference in diagnostic outcome.

A limitation of our trial is that most Chartis measurements under conscious sedation were carried out in the earlier studies, while at that point Chartis measurement performance experience was limited, possibly leading to a learning curve bias. A study by Herzog *et al.* for example described a 12% reduction of inconclusive Chartis measurements, due to increasing experience of the bronchoscopists, in a 5 year period (18). Another limitation of our study is that patients were retrospectively included from several trials, introducing a possible selection bias. On the other hand, we sequentially included all patients who underwent Chartis measurement in our center during the given timeframe and did not leave patients out of the analysis. In addition, we were able to include a large number of measurements compared to other retrospective studies investigating Chartis (14,18). Furthermore, all measurements were performed in one specialised treatment center with only two physicians performing the measurements, leading to a high level of standardisation.

In conclusion, in this retrospective study we observed significantly longer duration of the Chartis measurement as well as a higher number of attempts needed under conscious sedation compared to general anesthesia. This could indicate that the feasibility of the Chartis measurement is better under general anesthesia. The results of this study suggest advantages of performing Chartis measurement under general anesthesia, without losing diagnostic power. We recommend to perform a prospective trial comparing both techniques within the same patients to validate this approach.

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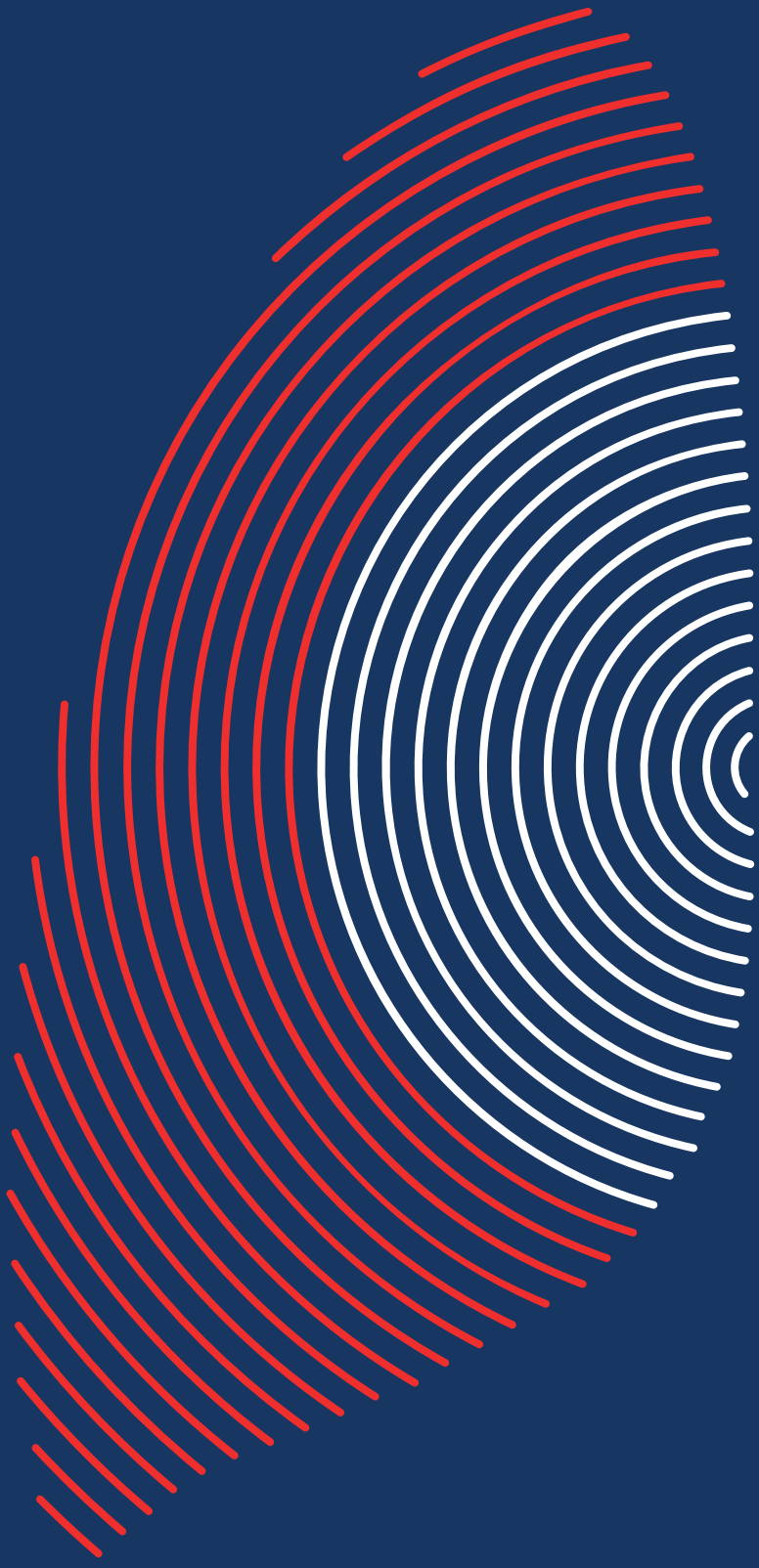

CHAPTER 7

Collateral ventilation measurement using Chartis: procedural sedation versus general anesthesia

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ABSTRACT

Background: Absence of interlobar collateral ventilation is key to successful endobronchial valve treatment in patients with severe emphysema and can be functionally assessed using the Chartis® measurement. Chartis has been validated during spontaneous breathing, undergoing procedural sedation (PS), but can also be performed under general anesthesia (GA). Performing Chartis under PS is often challenging because of coughing, mucus secretion and difficulties in maintaining an adequate level of sedation. The study objective was to investigate whether there is a difference in Chartis measurement outcomes between PS and GA.

Methods: In this prospective study patients underwent Chartis measurements under both PS and GA. Study outcomes were Chartis measurement duration, number of measurements, feasibility and success rate.

Results: We included 30 patients with severe emphysema (mean age 62 years and median FEV_1 29% of pred.). Chartis measurement duration was significantly longer under PS than under GA (mean 20.3±4.2 minutes versus 15.1±4.4, P<0.001). There was no difference in the number of measurements performed (median 2 (range 1-3) for PS versus 1 (1-3) for GA, P=1.00). Chartis measurement was more feasible during GA (median sum of all feasibility scores: 12 (range 6-26) for PS versus 7 (5-13) for GA, P<0.001), with no statistical difference in success rate: 77% of cases for PS versus 97% under GA, P=0.07.

Conclusion: This study shows that Chartis measurement under general anesthesia is faster and more feasible to perform compared to procedural sedation, without affecting measurement outcomes.

INTRODUCTION

Bronchoscopic lung volume reduction (BLVR) using endobronchial valves (EBV) is an effective and safe treatment for selected patients with severe emphysema (1–4). To achieve EBV treatment benefit, interlobar collateral ventilation (CV) must be absent, as the presence of CV prevents the desired atelectasis of the target lobe (5). The presence of CV can be assessed using indirect measurement techniques such as quantitative computed tomography fissure analysis and hyperpolarized gas magnetic resonance imaging or direct techniques such as collateral flow measurement during bronchoscopic assessment with the Chartis System® (Pulmonx Inc., Redwood City, CA, USA)(6,7). The Chartis system consists of a catheter which is designed to be advanced through the working channel of a flexible bronchoscope and uses an inflatable balloon at the tip of the catheter to selectively occlude the entrance of a lung lobe (see figure 1). The system measures flow from the occluded lobe and calculates the resistance to airflow through collateral channels and quantifies the amount of CV within a specific lobe (8).

Figure 1: Chartis measurement system.

In our BLVR treatment expert center, all patients scheduled for EBV treatment undergo a Chartis measurement to determine CV status. Chartis measurement was originally validated in patients breathing spontaneously undergoing procedural sedation (PS) (9). However, performing a Chartis measurement under PS can be very challenging because of problems with catheter placement caused by coughing reflexes of the patient, mucus secretions that can occlude the catheter, swelling of the airway mucosa causing challenging measurements and difficulties in maintaining a sufficient level of sedation. Although in several recent EBV trials as well as in our ongoing regular treatment program BREATH-NL (NCT02815683) we have performed Chartis measurement under general anesthesia (GA), the measurement has not yet been validated under GA (2–4). We recently published a retrospective analysis on this topic, suggesting advantages of Chartis measurement under GA with shorter procedure times and fewer measurements necessary, without a difference in target lobe volume reduction after EBV treatment (10). The objective of this study was to prospectively compare Chartis measurement under PS versus GA. We hypothesized that Chartis measurement under GA would result in faster procedures with higher physician assessed feasibility and with similar diagnostic outcome.

METHODS

Study design and participants

We performed a single center prospective study in which we included patients with severe emphysema (NCT03205826), who met the inclusion criteria for EBV treatment (5). For safety reasons, patients that met the following criteria were excluded from participation: forced expiratory volume in one second (FEV_1)<20% of predicted, residual volume/total lung capacity (RV/TLC) ratio >70%, pCO2>6.5 kPa at baseline at room air, right ventricular systolic pressure >40mmHg on echocardiogram, 6 minute walking distance <200 meter, known intolerance to lidocaine or any medical reason that warranted a short procedure.

The study was approved by the University Medical Center Groningen medical ethics committee (NL62374.042.17) and all patients provided written informed consent.

Procedure

CV status was evaluated in all patients using Chartis measurement under PS, followed by Chartis measurement under GA in the same procedure. The same lobes were assessed under PS and under GA. In all patients the measurements were performed in the target lobe for EBV treatment and when indicated the measurements were

also performed in the ipsilateral or secondary target lobes. Chartis measurement was terminated when either absence of collateral ventilation was confirmed by an airway flow gradually approaching zero (with airway resistance >10cm H_2O x ml/s for PS) in combination with immediate return of airway flow upon release of the balloon catheter (ruling out catheter obstruction), or when the presence of collateral ventilation was confirmed with the observation of a continuous, non-decreasing, expiratory airway flow during >6 minutes or totaling >1 liter (11,12). All Chartis measurements were performed by one interventional pulmonologist, who had previous experience with this measurement under PS and GA (DJS).

Anesthetic management

Anesthetic management consisted of two phases: PS and GA. Patient monitoring during both phases consisted of 3-lead ECG, SpO_2, non-invasive blood pressure monitoring, end-tidal CO_2 measurement and electroencephalography based depth of sedation monitoring using a BIS monitor (BIS VISTA®, Medtronic, Dublin, Ireland).

PS was induced using infusions of propofol and remifentanil. Propofol (20mg/ml) was administered by effect-site (Ce) targeted-controlled infusion (TCI) using the Schnider model with a starting target Ce concentration of 1 µg/ml (13). Remifentanil (50 µg/ml) was administered by effect-site (Ce) TCI using the Minto model starting at an initial target Ce of 1.0 ng/ml (14). Sedation depth was controlled primarily by adjusting the propofol target Ce concentration while the target remifentanil Ce was reduced on indication but rarely increased above 1.0 ng/ml. Lidocaine 10mg/ml was applied topically to the larynx by the interventional pulmonologist. Sedation was maintained in the time period between the PS phase and the GA phase.

In order to pre-oxygenate the lungs adequately for the induction of GA, patients were administered 100% O_2 through a tight fitting face mask while still under PS. After pre-oxygenation Ce-propofol and Ce-remifentanil were increased to induce GA, rocuronium-bromide 0.3-0.6 mg/kg was administered and endotracheal intubation was performed by the attending anesthesiologist using a cuffed Shiley™ Hi-contour Oral/Nasal Tracheal Tube (Covidien™, Mansfield, USA) with an internal diameter of 9mm. Thereafter GA was maintained with TCI-propofol and remifentanil and the patients lungs were mechanically ventilated. The primary ventilator settings were: volume controlled ventilation mode, fraction of inspired oxygen 50%, positive end-expiratory pressure 3cm H_20, tidal volumes of 4 to 6ml/kg, respiratory rate 10/min and an inspiratory:expiratory ratio of 1:3 to 1:4. The adjustment of these settings, to ensure patient-safety, was left to the discretion of the attending anesthesiologist.

Outcome measures

The primary outcome measure was the difference in duration of Chartis measurement between the sedation and GA. Secondary outcome measures were the time until the patient was sufficiently sedated to undergo Chartis measurement, success rate of Chartis measurement, number of measurements performed and qualitative feasibility assessment between the two anesthesia methods. The duration of the Chartis measurement was defined as the time between the start of the applicable anesthesia phase (PS or GA) and the withdrawal of the Chartis catheter from the bronchoscope after Chartis measurement. Start of PS phase was defined as the start of propofol or remifentanil. Start of the GA phase was defined as the increase of propofol and remifentanil dosage for induction of GA. The time until the patient was sufficiently sedated to undergo Chartis was defined as the time between start of the PS or GA phases and the first advancement of the Chartis catheter through the bronchoscope. Measurements were considered successful when collateral ventilation status was classified as either positive or negative. A single measurement was defined as the data collected between initiation and termination of the measurement on the Chartis console. Chartis measurement was only performed once per lobe per patient, unless a measurement was considered unsuccessful. Feasibility of the measurement was scored for both PS as well as GA by the physician performing the measurement, using a 1-10 visual analog scale, with lower scores indicating better feasibility. Five sub-scores were scored: presence of mucus, amount of coughing, degree of airway collapse, need for breathing instruction (for PS only) and measurement feasibility. We calculated the sum of all sub-scores to assess overall feasibility.

Statistical analysis

The sample size calculation was based on a previous study from our group, in which the average time of Chartis measurement was 1283±720 seconds under PS and 818±477 seconds under GA (10). A paired samples t-test was performed and to reach a power of 80% with an alpha level of 0.05 and considering a 10% drop-out rate, a total of 30 patients were required.

Differences in duration, time until the patient was sufficiently sedated to undergo Chartis, number of measurements and feasibility score outcomes of the Chartis measurement between PS and GA were analysed using a paired samples t-test in case of normal distribution or a Wilcoxon signed rank test in case of non-normal distribution of data. The difference in success rate between the anesthesia methods was analysed using McNemar's test. Confidence intervals for non-normally distributed data were determined using Hodges Lehmann Estimator. Statistical

analyses were performed using SPSS (IBM, New York, NY, USA). P-values<0.05 were considered statistically significant.

RESULTS

In total, 31 patients signed informed consent, of which in 30 patients Chartis measurements were performed between April 2018 and January 2019. One patient was excluded from further analysis because severe bronchitis was observed during bronchoscopy, leading to ineligibility for EBV treatment and therefore no Chartis measurement was performed. The remaining thirty patients were included in the final analysis (23% male, mean age 63±6 years and median FEV_1 29% (range 21-56) of predicted). Baseline characteristics can be found in table 1. All patients completed the study without unexpected anesthesia related complications or unexpected procedure related complications.

Table 1: Patient characteristics

Characteristics	
n	30
Female/Male (%)	77/23
Age (years)	62.8±5.7
BMI (kg/m^2)	23.9±3.9
Pack-years (years)	49 (15-126)
FEV_1%predicted (%)	29 (21-56)
RV%predicted (%)	227 (181-300)
RV/TLC (ratio)	0.6 (0.6-0.8)
pC02 in arterial blood gas (kPa)	5.3±0.6
6MWD (meter)	369 (120-477)
SGRQ total score (units)	54.7±11.0

Data are presented as mean ± standard deviation in case of normal distribution of data and as median(range) in case of non-normal distribution. BMI: Body mass index; FEV_1: forced expiratory volume in one second; RV: Residual volume; TLC: Total lung capacity; 6MWD: 6-minute walking distance; SGRQ: St. George's Respiratory Questionnaire.

A total of 48 Chartis measurements were performed under PS of which 19 were classified as CV negative and 10 were classified as CV positive. During 7 measurements we encountered a no flow state and 12 measurements were classified as unknown CV status. Forty-eight measurements were performed under GA of which 23 were classified as CV negative and 13 were classified as CV positive. During 10 measurements we encountered a no flow state and 2 measurements were classified as unknown CV status.

Chartis measurement took significantly longer under PS than under GA. In addition, with the patient under PS, it took significantly longer before the patient was sufficiently sedated to undergo Chartis compared to GA. No significant difference in the number of measurements performed was observed. The success rate of Chartis measurement was higher under GA compared to PS, however not statistically significant. Chartis outcomes are provided in table 2.

Discrepancies in CV status outcome between PS and GA were encountered in 4 measurements. Two measurements that were classified as CV positive under PS were, when measured in the same lobe of the same patient, classified as CV negative during GA, while two other measurements were classified CV negative under PS and CV positive under GA. Out of these 4 patients, 3 underwent EBV treatment and 1 patient was not treated based on a significant contribution of the occluded target lobe to the overall gas exchange of the patient. In one patient who was classified as CV positive under PS and as CV negative under GA, full lobar atelectasis was observed on high resolution computed tomography scan (HRCT) 6 weeks after EBV treatment. In two patients, who were classified as CV negative under PS and as CV positive under GA, treatment did not result in lobar atelectasis on HRCT at 6 weeks follow-up.

Chartis measurements were more feasible under GA compared to PS. During PS, mucus score, coughing score and measurement feasibility were significantly worse compared to GA, while airway collapse did not differ between both methods (table 2).

There was no difference in median Ce propofol during the start of Chartis measurement under PS versus GA. The median Ce remifentanil during the start of Chartis measurement was significantly lower during PS than during GA. The median BIS score at the time of start Chartis measurement was significantly higher during PS compared to GA. All patients were mechanically ventilated during the GA phase. The

median tidal volume was 5ml/kg (3-7) and the median plateau pressure observed was 18 cm H_20 (13-38). During PS, a mean of 294±55mg lidocaine was administered topically to the patients.

Table 2: Chartis measurement outcomes under procedural sedation and general anesthesia

	Procedural sedation	General Anesthesia	Difference	P-Value
Measurement				
Duration of total Chartis procedure per patient (minutes)	20.3±4.2	15.1±4.4	5.2 [3.4-7.1]	P<0.001
Time until patient was sufficiently sedated to undergo Chartis measurement (minutes)	12.5±3.0	7.6±1.8	4.9 [3.7-6.1]	P<0.001
Number of measurements per patient (number)	2 (1-3)	1 (1-3)	0 [0-0]	P=1.00
Success rate (%)	77%	97%	NA	P=0.07
Feasibility				
Sum of feasibility scores (score)	12 (6-26)	7 (5-13)	6 [4-8]	P<0.001
Mucus (score)	4 (2-8)	3 (1-5)	2 [1-3]	P<0.001
Coughing (score)	4 (1-8)	1 (1-1)	3 [2-4]	P<0.001
Airway collapse (score)	2 (1-8)	1 (1-4)	1 [0-1]	P=0.06
Feasibility (score)	3 (1-7)	2 (1-4)	1 [1-2]	P<0.01
Breathing instruction during procedural sedation (score)	2 (1-10)	NA	NA	NA
Anesthesia				
Propofol effect site concentration at time of start Chartis measurement (µg/ml)	3 (1-5)	3 (2-5)	-0.4 [-1-0.1]	P=0.09
Remifentanil effect site concentration at time of start Chartis measurement (ng/ml)	1 (1-2)	4 (2-5)	-3 [-3--3]	P<0.001
BIS score at time of start Chartis measurement (score)	76 (46-88)	39 (24-64)	35 [29-38]	P<0.001

Data are presented as mean ± standard deviation in case of normal distribution of data and as median (range) in case of non-normal distribution. The differences between the anesthesia methods are presented as mean or median [95% confidence interval]. Confidence intervals for non-normally distributed data were determined using Hodges Lehmann Estimator. Differences in outcomes between procedural sedation and general anesthesia were analyzed with a paired samples t-test in case of normal distribution of data or a Wilcoxon signed rank test in case of non-normal distribution of data. The difference in success rate of the measurements was analysed using a McNemar's test. NA: Not applicable. BIS: Bispectral index. Mucus, coughing, airway collapse, feasibility and breathing instruction were scored on a 0 to 10 scale, with a score of 0 indicating, no mucus, no coughing, no airway collapse, very feasible measurement and no breathing instruction, and a score of 10 indicating, large amounts of mucus, severe coughing, severe airway collapse, very unfeasible measurement and continuous breathing instruction necessary.

DISCUSSION

This first prospective study comparing Chartis measurement of CV under PS versus GA showed that Chartis measurement took significantly longer and was less feasible under PS compared to this measurement under GA. The performance of Chartis measurement was less feasible under PS, with more mucus and coughing problems. No statistical differences were found in the number of measurements or the measurement success rate.

Chartis measurement is an important tool used to assess interlobar CV status and achieve EBV treatment success, and should ideally be performed in circumstances that allow for fast and effective measurement, preferably in the same session in which the EBV placement is performed (5). The differences in duration and feasibility between PS and GA that we found are likely to be caused by more mucus production, causing catheter obstruction, or coughing resulting in problems with catheter positioning, as well as maintaining adequate sedation levels in the PS group, all causing more difficult measurement and interpretation of Chartis results.

The results of this study are in line with a retrospective analysis performed by our group in which longer and more frequent measurements under PS were observed, without a difference in target lobe volume reduction after EBV treatment (10). The nominal success rate of Chartis measurement in this study was higher for GA, but this difference was not statistically significant. In addition, and supportive of our findings, a recently published retrospective analysis by Thiruvenkatarajan *et al.* comparing PS and GA suggests better interventional conditions, patient comfort and reduced anesthetic time under GA (15).

No direct unexpected anesthesia related complications or direct unexpected procedure related complications were observed in our study. Thiruvenkatarajan *et al.* describe occurrence of mild hypotension periods during EBV treatment under GA, in line with expected blood pressure decline after induction of GA and responding to vasopressor bolusses. One case of severe hypotension in the same study was observed which was ascribed to possible anaphylaxis and led to procedure termination (15). Post-treatment expected complications were not registered for our study. In the recently published LIBERATE trial, post EBV treatment complications were compared between procedures performed under PS versus GA: chest pain occurred in 40% of patients under PS versus 18% under GA, pneumothorax occurred in 24% of patients under PS versus 33% under GA and COPD exacerbations were

observed in 22% of patients after PS versus 18% under GA, however no statistical testing was performed to compare the complication rates between the anesthesia methods. In the same trial, no difference in FEV_1 outcome after EBV treatment between the two anesthesia methods was found (4).

Next to the above mentioned disadvantages, performing Chartis under PS also has potential advantages over GA: lower dosages of medication are necessary and no intubation and mechanical ventilation is required. Even though the performance of Chartis measurement under GA is more resource intensive, invasive for the patient and sometimes unavailable in BLVR centers, the use of GA for Chartis measurement is advocated by an expert panel on BLVR (5).

A theoretical argument against the performance of Chartis under GA is that the use of positive pressure ventilation might open CV channels, which would not be open under spontaneous breathing circumstances, leading to a false positive CV outcome. In the current study we did not observe any relevant differences in CV status outcomes between PS and GA. This observation is further supported by our previously published retrospective analysis in which no difference in target lobe volume reduction outcome between the two methods was seen after EBV treatment (10).

Because patients in this study received PS before conversion to GA, the time needed to induce GA could have hypothetically been reduced and led to underestimation of the time before the patient was sufficiently sedated to undergo Chartis measurement. With the TCI-technique used in our institution, however, the time needed to increase remifentanil from PS to GA levels using target-controlled infusion is approximately 80 seconds while the time needed to achieve GA levels of remifentanil when starting from 0 is approximately 90 seconds. In other words, the sedation Ce's of propofol and remifentanil have not led to a significant reduction of the time needed to induce GA while in addition during the induction of GA, the anesthesiologist had to wait around 3 to 4 minutes for the neuromuscular blockade needed for tracheal intubation to take effect. Finally, all feasibility outcomes were scored by only one physician, which might lead to an observation bias. Furthermore, we only assessed physician feasibility, while ideally the experience of the patients should be taken in consideration as well. Unfortunately this is challenging to investigate as procedure related amnesia occurrence will lead to recall bias.

A strength of our study is that all Chartis measurements were performed by one interventional pulmonologist with experience with Chartis under both anesthesia techniques in one specialized treatment center, which increased standardization. In addition, all patients received both anesthesia techniques in a standardized fashion with medication dosage models and fixed ventilator settings. In our opinion, the fact that all patients received both PS as well as GA is a strength of our study. Ideally, the order in which patients undergo PS or GA first should be randomized, however we considered this approach unfeasible because of practical limitations.

In conclusion, we suggest performing Chartis measurement under general anesthesia because of higher feasibility and shorter procedure times compared to procedural sedation, without losing diagnostic power. The results from this study might result in more efficient and feasible Chartis measurement in future endobronchial valve treatment.

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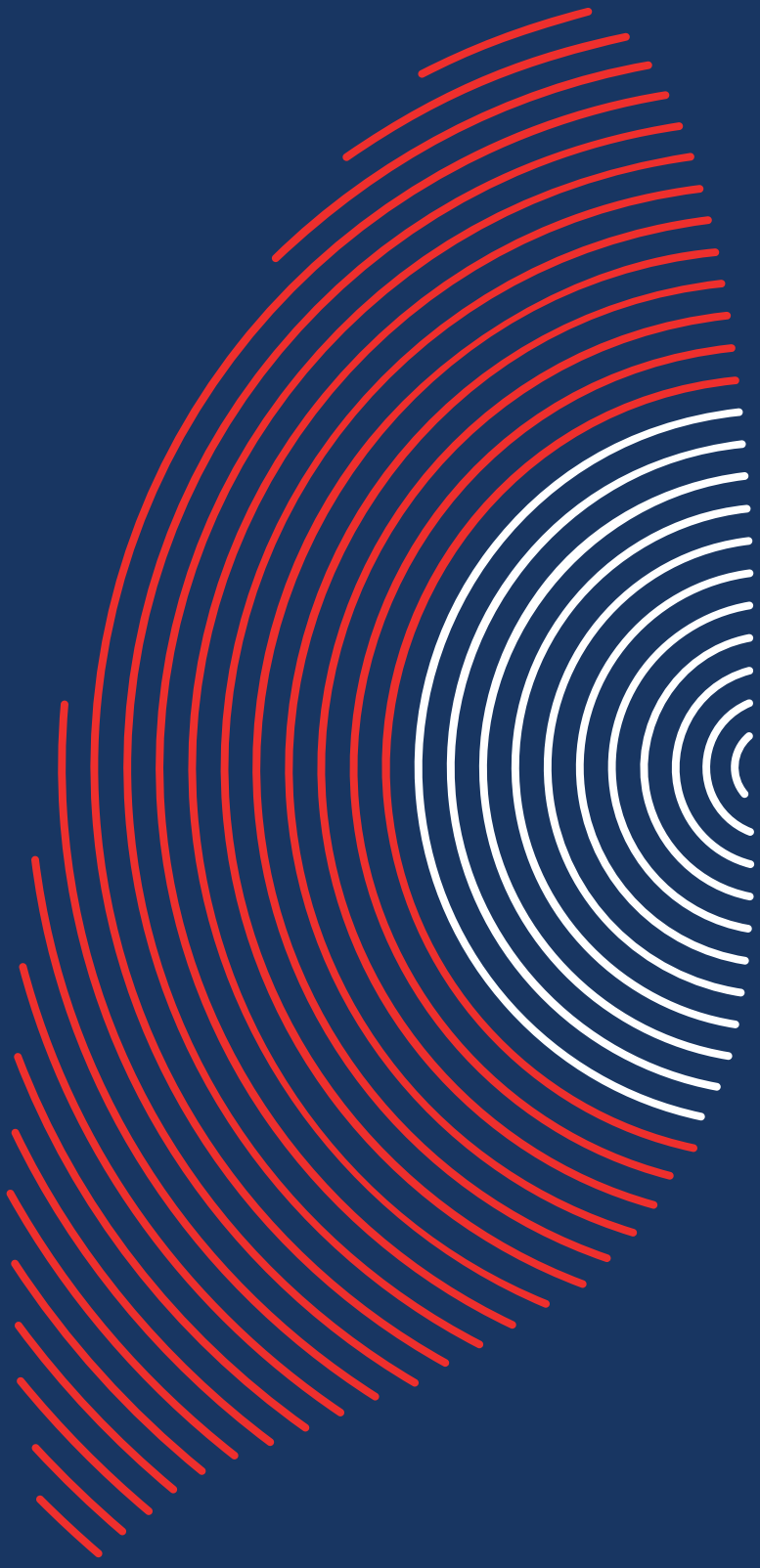

CHAPTER 8

Temporary right middle lobe occlusion with a blocking device to enable collateral ventilation measurement of the right major fissure

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ABSTRACT

Background: Absence of interlobar collateral ventilation is essential to achieve lobar volume reduction after endobronchial valve treatment (EBV) and can be assessed using the Chartis measurement. However, especially in lower lobe measurements, Chartis can be complicated by the 'no flow phenomenon', during which a sudden cessation of flow is observed, leading to an unreliable measurement. If this phenomenon occurs in the right lower lobe, when measuring collateral flow over the right major fissure, the entrance to the right middle lobe should be occluded and the Chartis balloon should be placed in the right upper lobe. Both Watanabe spigots and balloon catheters can be used to achieve occlusion.

Methods: We performed a retrospective analysis of patients scheduled for EBV treatment in an EBV registry between 09/2016 and 09/2019.

Results: We included 15 patients with severe emphysema (median age 63 (range 47-73) years, 73% female and FEV_1 24% (19-36) of predicted), who required temporary middle lobe occlusion (12 Watanabe spigot/3 balloon catheter). After occlusion, a reliable Chartis outcome was obtained in all patients.

Conclusion: Temporary middle lobe occlusion using a blocking device is helpful in obtaining a reliable Chartis outcome in case of a right lower lobe no flow phenomenon.

INTRODUCTION

The absence of interlobar collateral ventilation is essential to achieve lobar volume reduction with endobronchial valve (EBV) treatment in patients with severe emphysema and can be assessed using the Chartis® (Pulmonx, USA) measurement (1–4). Chartis measurement can be complicated by the 'no flow phenomenon', in which dynamic expiratory airway collapse is believed to cause a sudden cessation of flow during measurement, leading to an unreliable Chartis measurement (5). Literature shows that this can occur in up to a third of all measurements and most frequently affects the lower lobes (5–7). Normally, Chartis measurement is performed in the lobe selected for treatment with EBV. When the no flow phenomenon occurs during measurement in the left lung, measurement in the adjacent lobe can easily be performed to assess the integrity of the left major fissure (8). However, in case of no flow in the right lower lobe, measurement of the right upper lobe may not be reliable because collateral flow originating from the right middle lobe, due to common incompleteness of the right minor fissure, can result in false positive Chartis outcomes (1). If the middle lobe is not occluded, the measurement in the right upper lobe only measures the collateral flow over the right upper lobe fissure (part of the major fissure and minor fissure) and not the right major fissure.

METHODS

We performed a retrospective analysis, in which we included all patients with the right lower lobe as primary EBV target and in which the no flow phenomenon occurred during Chartis measurement in the right lower lobe.

All patients were scheduled for treatment in the Dutch national EBV treatment registry (BREATH-NL) between 09/2016 and 09/2019 (Clinicaltrials.gov identifier: NCT02815683). Chartis measurements were performed in all patients regardless of fissure integrity scores. The presence of collateral ventilation was confirmed when a continuous, non-decreasing, expiratory airway flow was observed during >6 minutes or earlier with a similar pattern when totaling >1 liter (8). Every patient underwent Chartis measurement under general anesthesia using a previously described approach (9). Target lobe volume and fissure integrity were assessed using the StratX quantitative CT Platform (Pulmonx, USA). 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 ethical approval was not needed. All patients provided written informed consent.

To achieve the desired temporary occlusion of the right middle lobe, both Watanabe spigots® (Novatech, France) and Extractor® Pro retrieval balloon catheters (Boston Scientific, United States), were used. The Watanabe spigot (figure 1) is a silicon bronchial filler, which is frequently used for persistent pneumothorax, hemoptysis and bronchopleural fistula, and is available in three sizes: 5, 6 and 7mm diameter (10). The retrieval balloon (figure 2) can be inflated to any desired diameter between 5 and 20mm and can be replaced by any local available alternative balloon.

Our primary outcome was the success rate of right upper lobe Chartis measurement of the right major fissure after occlusion of the right middle lobe and placement of the Chartis balloon in the right upper lobe. Our secondary outcome was the amount of target lobe volume reduction after EBV treatment.

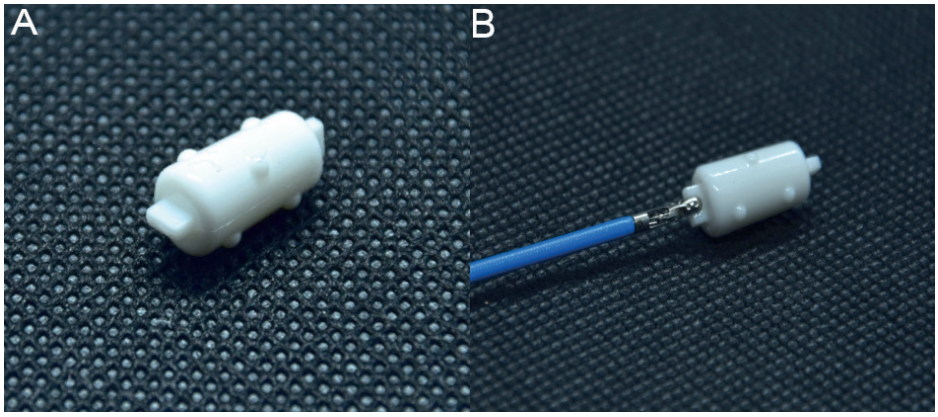

Figure 1: Panel A: Watanabe spigot. Panel B: Watanabe spigot held by biopsy forceps, which can be used for both placement and removal of the spigot.

Case report

A 63 year old female with severe emphysema (forced expiratory volume in 1 second (FEV_1) 25% of predicted and residual volume (RV) 214% of predicted) was scheduled for EBV treatment in our hospital. The pre-determined target for treatment was the right lower lobe (51% of voxels <-950 Hounsfield Units). We were initially unable to obtain a reliable Chartis measurement in the right lower lobe, as we encountered the no flow phenomenon (figure 3A). After the occlusion of the right middle lobe with a Watanabe spigot, we performed a Chartis measurement in the right upper lobe which indicated absence of interlobar collateral ventilation of the right major fissure (figure 3B). Subsequently, five endobronchial valves were placed in the right lower lobe. Six weeks after treatment, the patient achieved a target lobe volume

reduction of 1201ml, had an FEV_1 of 40% of predicted (69% relative increase) and an RV of 148% of predicted (31% relative reduction).

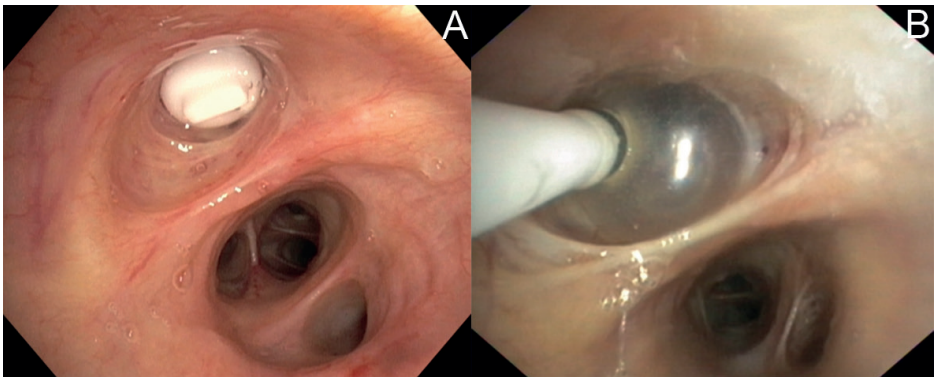

Figure 2: Panel A: Watanabe spigot occluding the entrance of the right middle lobe. Panel B: Balloon catheter occluding the entrance of the right middle lobe.

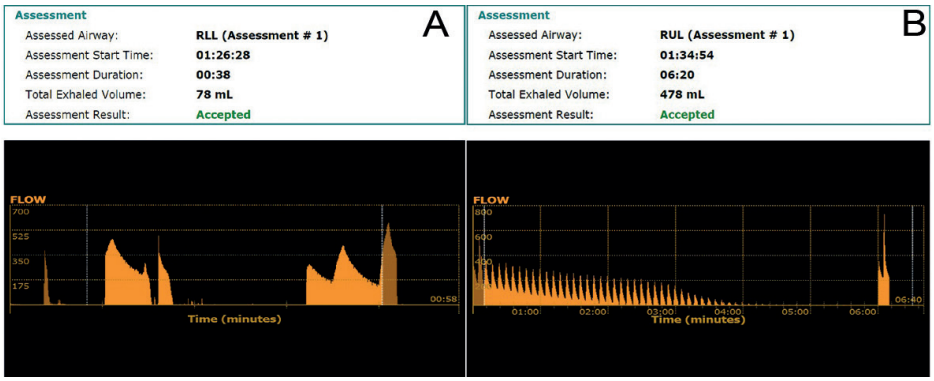

Figure 3: Panel A: Chartis measurement output indicating no flow phenomenon in the RLL. The initially present flow becomes zero after the balloon seal is achieved, flow returns when the catheter is withdrawn with subsequent loss of balloon seal, ruling out other potential causes of no flow. Panel B: Chartis measurement output of the RUL in the same patient, indicating absence of interlobar collateral ventilation after occlusion of the RML with a Watanabe spigot.

Case Series

Out of the 220 EBV cases, 36 patients (16%) had the right lower lobe as primary target for EBV. In 15 out of these 36 cases (42%) we performed a temporary right middle lobe occlusion with either a Watanabe spigot or balloon catheter in order to perform Chartis measurement of the right major fissure.

Therefore, 15 patients were included in the analysis (73% female, median FEV_1 24% of predicted) (baseline characteristics are presented in table 1). Temporary right middle lobe occlusion was successful in all patients. The Watanabe spigot was used in 12 cases. In 3 cases the balloon catheter was used because the use of the Watanabe spigot was not possible, because of a relatively large diameter entrance to the right middle lobe.

Table 1: Patient characteristics

Patient characteristics	
Number of patients	15
Female/Male (%)	73/27
Age (years)	63 (47-73)
BMI (kg/m^2)	22 (19-30)
Packyears (years)	43 (10-85)
FEV_1 predicted(%)	24 (19-36)
RVpredicted (%)	229 (187-317)
RV/TLC (ratio)	0.65 (0.58-0.76)
6MWD (meter)	320 (15-484)

Data are presented as median (range) unless otherwise indicated. BMI: Body mass index; FEV_1: forced expiratory volume in one second; RV: Residual volume; TLC: Total lung capacity; 6MWD: 6-minute walking distance.

In all patients a reliable Chartis measurement could be performed after we placed the blocking device, and we did not observe a no flow phenomenon. In 13 out of 15 patients (87%), the Chartis measurement in the right upper lobe indicated absence of collateral ventilation of the right major fissure. Six weeks after treatment, the median reduction in target lobe volume was 863ml and 9 out of 13 patients (69%) had achieved the minimal important difference for target lobe volume reduction of 563ml (11). See table 2 for Chartis measurement outcomes.

Table 2: Chartis measurements

Chartis measurements	
Total EBV cases (number)	220
Cases with RLL as primary EBV target (number)	36
Cases where temporary RML occlusion was indicated (number(%))	15 (42%)
Blocking device used	
Watanabe spigot (number)	12
Balloon catheter (number)	3
Chartis measurement outcome right major fissure (CV negative/ CV positive)	13/2
Target Lobe Volume at baseline (ml)	1625 (1027-3001)
Target Lobe Volume Reduction at 6 weeks after treatment (ml)	-863 (-3001-5)
Right major fissure integrity (%)	99 (95-100)
Right minor fissure integrity (%)	91 (58-98)

Data are presented as median (range) unless otherwise indicated. RML: Right middle lobe; EBV: Endobronchial valve. CV: collateral ventilation.

DISCUSSION

This case series provides insight in the use of two different approaches to temporary right middle lobe occlusion: Watanabe spigots and balloon catheters, to achieve reliable Chartis measurement outcomes. Using this technique, we were able to confirm the presence or absence of interlobar collateral ventilation of the right major fissure in all our patients, after initial measurement of the right lower lobe had failed. We considered both the insertion and removal of the Watanabe spigot and balloon catheter very feasible (see video in study supplement). While not structurally assessed in this case series, use of the blocking devices did not prolong Chartis measurement for more than several minutes. Although both blocking device approaches were feasible, in our practice, we generally reserve the use of a balloon catheter for patients with a relatively wide right middle lobe entrance, given its larger potential diameter (5-20mm) than the Watanabe spigot (5-7mm).

While temporary right middle lobe occlusion was already recommended by the 2017 expert panel recommendations on EBV treatment, to the best of our knowledge no data was previously published on this technique (8).

Before the absence of flow during Chartis measurement is attributed to the no flow phenomenon, we recommend excluding other causes of absent flow: mucus impaction of the Chartis catheter should first be ruled out by flushing of the catheter,

and in addition correct catheter positioning should be verified. The catheter tip should not be in direct contact with the airway wall. While different terminology is used in the literature to describe the no flow phenomenon: for example “low flow” and “collapse phenomenon”, we suggest to describe this problem as the no flow phenomenon, as this description describes the clinical observation during measurement (5,7).

Previous studies have attributed the no flow phenomenon to dynamic expiratory airway collapse, in which airway collapse distal of the inflated Chartis balloon prevents expiratory airflow (5,7). While we consider this to be a valid explanation, the question remains why the lower lobes are more often affected by this phenomenon. A possible explanation may be the transpulmonary pressure gradient from the apical zones to the basal zones in combination with the emphysematous lung tissue. More research is required to confirm the exact physiological mechanism causing this phenomenon and its lower lobe predominance.

In conclusion, selective temporary occlusion of the right middle lobe using a blocking device, is helpful in obtaining a reliable Chartis outcome in case of the no flow phenomenon in the right lower lobe. The application of this simple technique may improve patient selection and outcomes for EBV treatment.

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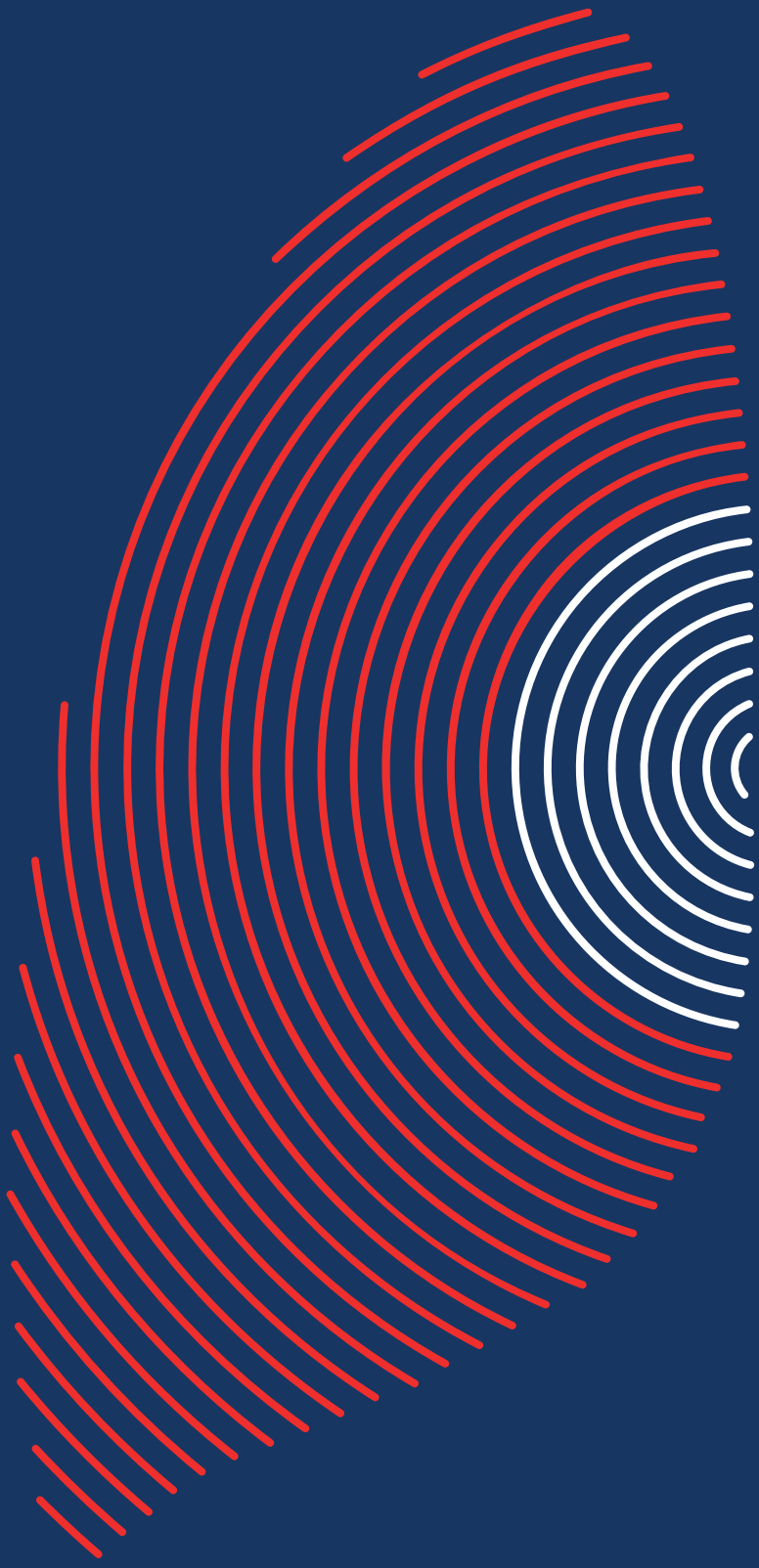

CHAPTER 9

The minimal important difference for the St. George's Respiratory Questionnaire in patients with severe COPD

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ABSTRACT

Background: The St. George's Respiratory Questionnaire (SGRQ) is a validated, commonly used questionnaire for measuring quality of life in patients with chronic obstructive pulmonary disease (COPD). The current established minimal important difference (MID) for SGRQ in an average COPD population is -4 units. However, for patients with severe COPD, the MID has not been thoroughly validated.

Objective: The objective of this study was to re-determine the MID for the SGRQ in patients with severe COPD.

Methods: We retrospectively included patients who participated in seven different bronchoscopic lung volume reduction clinical trials. Anchor- and distribution-based methods were used to define the MID for SGRQ. FEV_1, 6-minute walk distance and residual volume were used as anchors.

Results: 115 severe COPD patients (mean ± SD, FEV_1 26 ± 9% predicted, SGRQ 62 ± 11 units), Combining both anchor- and distribution-based methods, we identified a SGRQ MID of -8.3 units at 1 month and -7.1 units at 6 months.

Conclusions: This study proposes an alternative SGRQ MID for patients with severe COPD of -8.3 units at 1 month and -7.1 units at 6 months follow-up after intervention. Our new MID estimates could be applied for both interpreting SGRQ outcomes as well as sample size determination in future clinical trials investigating interventions in severe COPD patients.

INTRODUCTION

The St. George's Respiratory Questionnaire (SGRQ) is a widely used, self-reported, quality of life assessment method to evaluate obstructive airways disease and especially Chronic Obstructive Pulmonary Disease (COPD) (1). When evaluating different treatment options for COPD it is relevant to investigate whether a statistically significant improvement is also clinically relevant. A method to describe this relationship is called the minimal important difference (MID) (2).

A decrease of 4 units, after a medical intervention, in the SGRQ score is generally accepted in the literature to be a valid threshold value of beneficial treatment (3). This threshold, or MID, is broadly applied in the evaluation of COPD-treatment for patients with a wide range of disease severity. However, patients with severe COPD have not been specifically included in previous MID calculations, knowing that their baseline SGRQ total scores are very high, making a 4-unit drop easy. In our own clinical experience, many patients with severe COPD improve more than 10 units after bronchoscopic lung volume reduction treatment (4–6). Therefore, the established 4-unit MID for SGRQ might not be fully applicable to the severe COPD patient group. We hypothesised that the MID for SGRQ is higher in patients with severe COPD.

The objective of this study was to determine the MID of SGRQ in patients with severe COPD.

METHODS

Study design

We performed a retrospective analysis on data from 7 completed bronchoscopic lung volume reduction (BLVR) clinical trials conducted in one hospital in the Netherlands (University Medical Center Groningen). Patients were treated with either airway bypass stents (www.clinicaltrials.gov identifier number: NCT00391612) (7)), coils (NCT01220908 (4) & NCT01328899 (8) & NCT01421082 (9)), valves (NCT01101958 (6)) or foam-sealant (NCT01449292). Two trials (NCT00391612 (7) & NCT01101958(6)) included a control group and in total 19 control patients were included in our analyses. All trials had prior approval from the local medical ethical committee and all patients provided informed consent before participating. Patients were included in the analysis when 1 and/or 6 months post-treatment follow-up of the SGRQ assessment was available for evaluation.

MID calculation

Both the anchor-based as well as the distribution-based methods for determining the MID were used. For the anchor-based method, where the change in SGRQ outcome is compared to an established MID (2), the anchors chosen were: the forced expiratory volume in 1 second (FEV_1)(MID 100ml (10)), 6-minute walk distance (6MWD)(MID 26 meters (11)) and Residual Volume (RV) (MID 400ml (12)).

Distribution-based methods compare the change in outcome measure with some measure of variability (2). In this study, Cohen's effect size was used, which is a frequently used distribution-based method in studies establishing MID's in pulmonary medicine (11–13) and is one of the distribution-based methods recommended in the literature (2,14).

We calculated the final MID on basis of both the anchor- and distribution-based methods. The combined MID was calculated using the average of the 3 anchor-based and 1 distribution-based MID's, each counting for 25% weight).

Measurements

The SGRQ consists of three subscales and a total score. Scores on SGRQ range from 0 to 100, with higher scores indicating worse quality of life. The total score summarizes the impact of the disease on overall health status (15). At baseline, 1 month and 6 month follow-up the SGRQ was completed. Furthermore, spirometry and bodyplethysmography (Masterscreen™, Viasys, Germany) were performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (16,17) and a 6-minute walk test was performed according to the American Thoracic Society guidelines (18).

Data analysis

The absolute and relative change at 1 and 6 months follow-up compared to baseline were calculated. Pearson correlation coefficients (data were normally distributed) were calculated to test whether the univariate association between change in SGRQ score and change in anchor scores was sufficient to perform the anchor-based method. A linear regression analysis was performed with change in SGRQ score as dependent variable and change in anchor score as independent variable. Afterwards, we entered the anchor-MID into the equation derived from the linear regression analysis. Subsequently, the MID could be calculated from the established equation. For the distribution-based method a moderate (0.5) Cohen's effect size was calculated of the change score of SGRQ from baseline to 1 and 6 months follow-

up. P-values <0.05 were considered significant. Statistical analyses were performed using IBM SPSS statistics version 22 (IBM, New York, USA).

RESULTS

115 patients had a baseline SGRQ measurement in combination with either a 1 or 6 months follow-up SGRQ measurement and were included in the analyses. 110 patients were included in the 1 month follow-up analysis and 86 patients were included in the 6 months follow-up analysis (see figure 1 for study flowchart).

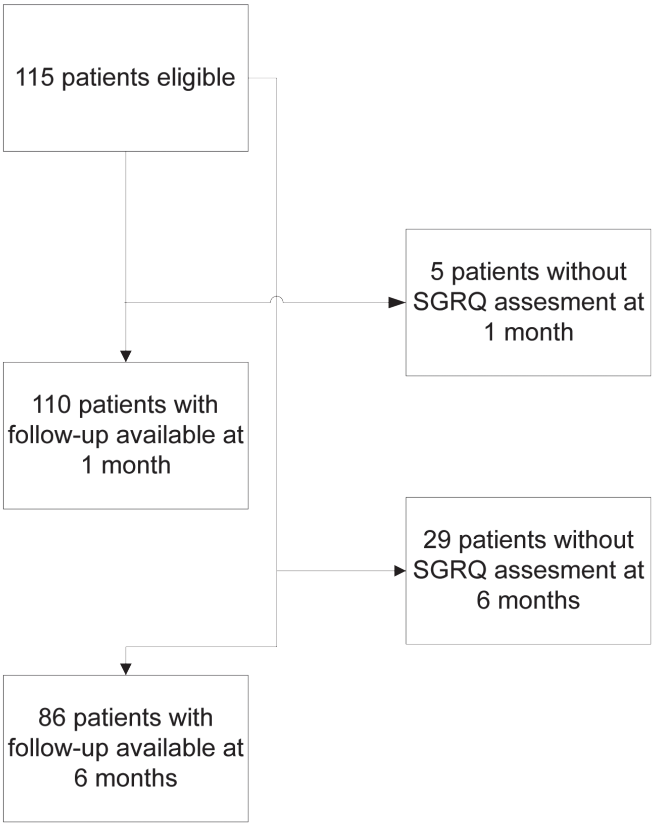

Figure 1: Patient flowchart. SGRQ: St. George's Respiratory Questionnaire.

Patient characteristics at baseline and change scores after 1 and 6 months follow-up are shown in table 1. At baseline, mean FEV_1 was 26 ± 9% of predicted and the SGRQ total score was 62 ± 11 units.

Table 1: Patient characteristics at baseline and change at 1 and 6 months follow-up

	Baseline (n=115)	% Predicted at Baseline (n=115)	Δ1 month from baseline (n=110)	Δ6 months from baseline (n=86)
Females/Males	73/42	NA	NA	NA
Age (years)	60±8.8	NA	NA	NA
BMI (kg/m^2)	24±3.6	NA	0.3±0.8	0.5±1.1
6MWD (meters)	311±95	NA	38.5±60.7	38.2±68.5
SGRQ Total score (units)	62±10.9	NA	-9.8±13.8	-7.5±15.8
Packyears (years)	36±17	NA	NA	NA
RV (liter)	4.9±1.1	241±46.7	-0.5±0.6	-0.5±0.6
FEV_1 (liter)	0.7±0.3	25.9±9.0	0.1±0.2	0.1±0.2
TLC (liter)	7.7±1.4	136±14.6	-0.2±0.4	-0.25±0.4
RV/TLC%	64.6±7.7	168±22.2	-4.0±5.7	-4.1±6.3

Data are presented as number or mean ± SD. Δ=change between baseline and follow-up. BMI: body mass index; FEV_1: forced expiratory volume in 1 second; 6MWD: 6-minute walk distance; SGRQ: St George's Respiratory Questionnaire; RV: residual volume; TLC: total lung capacity; NA: not applicable.

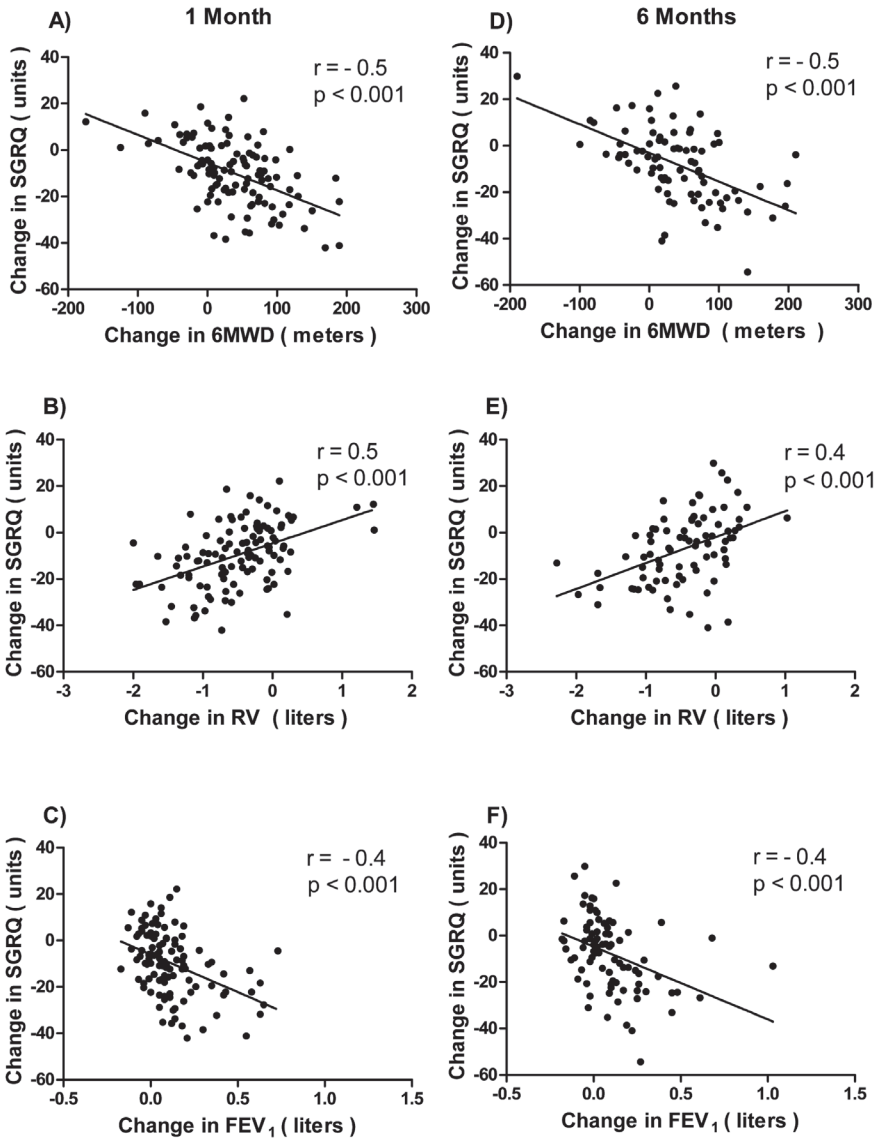

Figure 2: Scatterplots of 6-minute walk distance (6MWD), RV (Residual Volume) and forced expiratory volume in 1 second (FEV_1) versus St. George's respiratory questionnaire (SGRQ) at 1 and 6 months follow-up. Panels A to C correspond to 1 month follow-up, panels D to F correspond to 6 months follow-up.

An association of r≥0.4 (P<0.05) was found between the change in SGRQ and change in all three anchors (see figure 2).

The outcomes of the calculations for the anchor-based, distribution-based and combined methods at 1 and 6 month follow-up are shown in table 2. At 1 month follow-up we calculated a MID for SGRQ of each anchor: RV -8.7 (relative -13.8%), FEV_1 -9.2 (-13.0%) and 6MWD -8.5 (-15.3%). At 6 months follow-up we calculated a MID for RV of -6.4 (-10.2%), FEV_1 -7.8 (-11.5%) and 6MWD -6.3 (-9.2%). With the distribution-based method, we calculated a MID for SGRQ at 1 month follow-up of -6.9 units (relative -11.3%) and at 6 months follow-up of -7.9 units (relative -13.3%). Our combined MID (average of the 3 anchor-based and 1 distribution-based MID's) proved -8.3 units (relative -13,4%) at 1 month and -7.1 units (relative -11.1%) at 6 months.

Table 2: Minimal Important Differences for SGRQ

	Absolute SGRQ MID 1 month (unit)	Relative SGRQ MID 1 month (%)	Absolute SGRQ MID 6 months (unit)	Relative SGRQ MID 6 months (%)
Anchor-based				
RV	-8.7	-13.8%	-6.4	-10.2%
FEV_1	-9.2	-13.0%	-7.8	-11.5%
6MWD	-8.5	-15.3%	-6.3	-9.2%
Distribution-based:	-6.9	-11.3%	7.9	-13.3%
Combined:	-8.3	-13.4%	-7.1	-11.1%

Data are presented as SGRQ units or percentage change compared to baseline. MID: Minimal Important Difference; SGRQ: St. George's Respiratory Questionnaire; RV: residual volume; FEV_1: Forced expiratory volume in 1 second; 6MWD: 6-minute walk distance.

DISCUSSION

To our knowledge, we established for the first time, a MID for SGRQ specifically for patients with severe COPD. Our findings differ substantially from the MID for SGRQ of -4 units that has been described more general in COPD (3). Our results showed that the MID for patients with severe COPD was -8.3 units at 1-month follow-up and -7.1 units at 6-months follow-up. The relative MID was -13.4% at 1-month follow-up and -11.1% at 6-months follow-up.

Our calculated MID for SGRQ for patients with severe COPD significantly differed compared to the earlier established MID (3). One explanation could be the chosen time points. In the article of Jones *et al.* it is not clear for which time point the MID for SGRQ was determined (3). Whilst inconclusive, most of their methods to establish the

MID are applied at the 12 month follow-up interval. In contrast, our MID estimations are established at the short term, after 1 and 6 months follow-up. At 6 months follow-up interval the established MID was lower compared to the 1 month follow-up interval. It can be hypothesized that the diminished perceived effect of treatment results in lower decrease of SGRQ scores after 6 months follow-up. In the long-term a MID could be further decreased due to the progressive nature of COPD. For example, although treatments may produce an initial improvement in SGRQ, scores may subsequently return to the baseline level or worse due to disease progression (19,20). More research is needed to investigate whether the MID in severe COPD patients at 12 months follow-up differ from our findings at 1 and 6 months follow-up.

Our study population consisted of patients who were treated with BLVR and the question rises whether our newly established MID is only applicable to this treatment or to other treatment modalities for patients with severe COPD as well. There is no consensus on whether a MID is applicable to a specific treatment or a broad range of treatment modalities. Jones states that MID's were originally not developed in the context of specific treatments (21). He stated that the reference point (at least with anchor-based methods) is patient- or clinician-perceived benefit (21). Troosters *et al.* however question whether MID's based on anchor techniques can be used across different interventions as several processes may underlie the observed effects of interventions. For example, the expectations of patients may be different, yielding different effect sizes with different interventions (22). Therefore, more research is needed regarding the specificity of MID's for different treatments.

Several methods for estimating MID's have been described in the literature, the most important being anchor-based and distribution-based methods (14). The combination of multiple methods is generally recommended to increase reliability of outcome (14). Therefore, we relied on both anchor-based and distribution-based methods. The anchor-based method requires that a reasonably strong linear relationship exists between the anchor and the variable of interest (23). However, there is no consensus on how strong this relationship should be exactly. One review recommends statistically significant ($p<0.05$) correlation coefficients of ≥ 0.3 as appreciable (14) and two studies in COPD patients performed the analyses when correlation coefficients were 0.3 or 0.5 (11,24). In line with our previous study we chose a correlation coefficient threshold ≥ 0.4 (12). Distribution-based methods are commonly considered inferior to anchor-based methods because they rely solely on statistical criteria and depend heavily on the characteristics of a particular study (23). We agree with the general consensus that the distribution-based method

should only be used to support estimates derived from anchor-based methods (2,14). Therefore, we have placed less weight on the distribution-based method in calculating our combined MID.

When performing an anchor-based analysis the quality of the anchors can influence the outcomes. A good anchor, in our opinion, is present if it is derived from several studies with comparable patient populations, in our case severe COPD patients. The anchor should be determined using several methods. Finally, there should be an appreciable association between the outcome variable and anchor (23). Here we will evaluate the strengths and weaknesses of the three anchors we used for our analysis. The 6MWD MID estimate was determined in a study investigating the effect of lung volume reduction surgery in severe COPD patients (11). Therefore, the patient population was quite comparable to ours but a different intervention was performed. Another study, which investigated the MID for 6MWD, found a similar outcome for treatment with pulmonary rehabilitation (24). This 6MWD anchor was moderately correlated with SGRQ scores in our study (r =0.5). The MID for RV was established in almost the same population as we used (93 patients overlap) and therefore is not the best anchor for establishing our MID (12). The MID was determined in one single study and to increase the reliability we feel it should be retested in more studies. The MID for RV was moderately associated with SGRQ (r =0.4). A positive feature of the MID for FEV_1 is that it was determined in several studies comprising general COPD populations (10). A downside was that determining the MID of FEV_1 was never the primary objective of these studies (10). In our study, FEV_1 was moderately associated with SGRQ scores (r =0.4). In contrast to the anchor-based MID's, the distribution-based MID's were found to be higher at 6 months follow-up than at 1 month follow-up. This can be explained by the fact that, inherently to their methodology, distribution-based methods depend highly on variance in population. On 6 months follow-up the variance of measurements in the population is larger, leading to a higher distribution-based MID at 6 months, making it a more time-dependant method than the anchor-based method.

A limitation of our study is that most of our included studies were non-controlled. Another limitation of our study is that all our patients participated in trials investigating a BLVR treatment which is known to be a highly effective intervention resulting in a large decrease in SGRQ scores after treatment (25). This could affect the size of the MID estimates. Future studies, compromising multiple treatment-modalities other than BLVR, are needed to confirm our findings.

A strength of our study is that we were able to maintain a high level of standardization since all measurements were performed in one specialized research hospital in the Netherlands, applying the same settings/measurement sequence, using the same equipment. Furthermore, we had a, compared to most other MID determination studies, relatively large sample size (12,13,24).

In most studies determining a MID, results are solely expressed as absolute numbers. In our study we have also determined the relative MID's. Relative MID's are able to evaluate changes adjusted for baseline SGRQ-scores. We believe that when calculating a MID, besides the absolute MID also the relative MID should be estimated.

In conclusion, this study is the first to establish a MID SGRQ specifically for patients with severe COPD. Using a combination of anchor- and distribution-based methods we established a MID 1 month after treatment of -8.3 units and a MID of -7.1 after 6 months. The relative MID 1 month after treatment was -13.4% and after 6 months -11.1%. Our new MID estimates could be applied for both interpreting SGRQ outcomes as well as sample size determination in future clinical trials investigating severe COPD patients.

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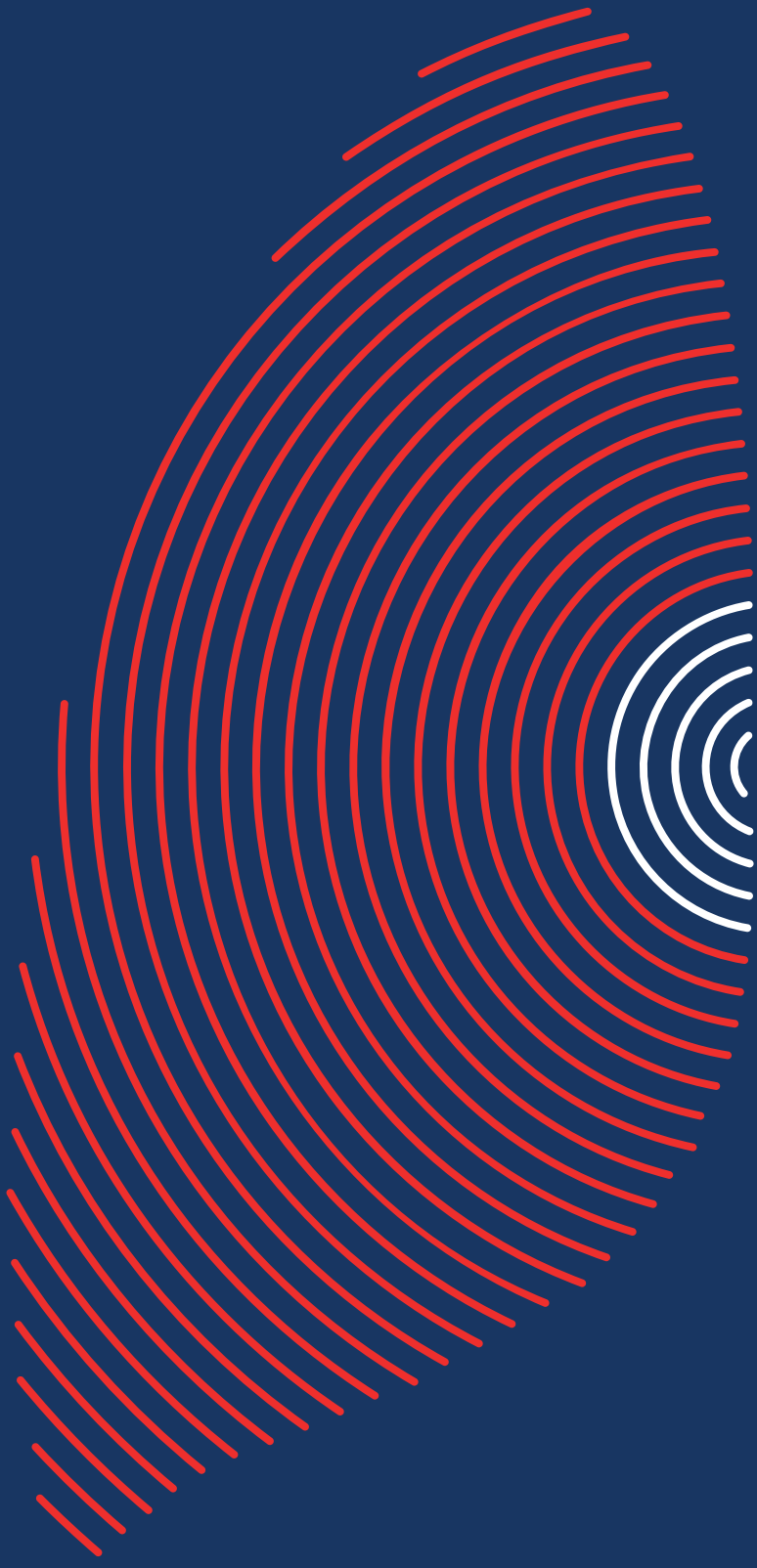

CHAPTER 10

Minimal important difference of target lobar volume reduction after endobronchial valve treatment for emphysema

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ABSTRACT

Background: Target lobar volume reduction (TLVR) is an important efficacy outcome measure for bronchoscopic lung volume reduction (BLVR) treatment using one-way endobronchial valves (EBV) in patients with severe emphysema. The commonly used cut-off value for TLVR that expresses a percievable clinical benefit is -350ml. However, a scientifically determined minimal important difference (MID) for TLVR never has been published.

Objective: The objective of this study was to determine the MID for TLVR on HRCT in patients who were treated with EBV.

Methods: A total of 318 severe emphysema patients from 2 BLVR trials were analysed. Anchor-based methods were used to define the TLVR MID at 6 months follow-up. Forced expiratory volume in 1 second (FEV_1), residual volume (RV) and St. George's Respiratory Questionnaire (SGRQ) were used as anchors.

Results: The calculated TLVR MID with each anchor was: FEV_1 –587ml, RV –534ml and SGRQ -560ml. The combined MID (average of the 3 anchor-based MID's) was –563ml.

Conclusions: Using the anchor-based method we established a TLVR MID of -563ml in patients with severe emphysema at 6 months follow-up after EBV treatment. This value can be useful for both interpreting the results from trials and clinical practice, as well as for designing future studies on lung volume reduction.

INTRODUCTION

Patients with severe emphysema do not respond well to the current regular treatment options. Bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBV) is a valid treatment option for patients with severe emphysema and proven absence of collateral ventilation. BLVR treatment using EBV shows high efficacy and an acceptable safety profile (1–3). The purpose of EBV is to induce atelectasis in the most diseased lobe ("target lobe") (figure 1). Like in surgical lung volume reduction, this approach reduces hyperinflation, resulting in improved function of the diaphragm and chest wall mechanics and consequent relief of dyspnea (4,5). The amount of target lobar volume reduction (TLVR) measured with high resolution computed tomography scans (HRCT) is one of the most important outcome measures of BLVR treatment using EBV since it has been shown to be an important predictor for clinically meaningful changes after this treatment (6).

The currently accepted, but solely expert opinion based, cut-off value for TLVR to reflect a meaningful clinical effect is a reduction of at least 350ml (7) using quantitative HRCT analysis, this was established on the basis that in the "VENT trial" the maximum TLVR in the control group receiving standard medical care rarely exceeded this level (8). To our knowledge, an objectively calculated minimal important difference (MID) for TLVR never has been published. In this respect the MID refers to the minimal TLVR that associates with significant improvements in clinically relevant outcomes of severe emphysema (9). We have seen many patients with severe emphysema improving far more than the 350ml cut-off value after BLVR treatment (1,7,10) and observed that the improvement might need to be more than the currently quoted 350ml to be appreciated by patients. Therefore, we hypothesized that the MID for TLVR is higher than the 350ml threshold in patients with severe emphysema.

The objective of this study was to determine the MID for TLVR in patients with severe emphysema who underwent BLVR treatment using EBV.

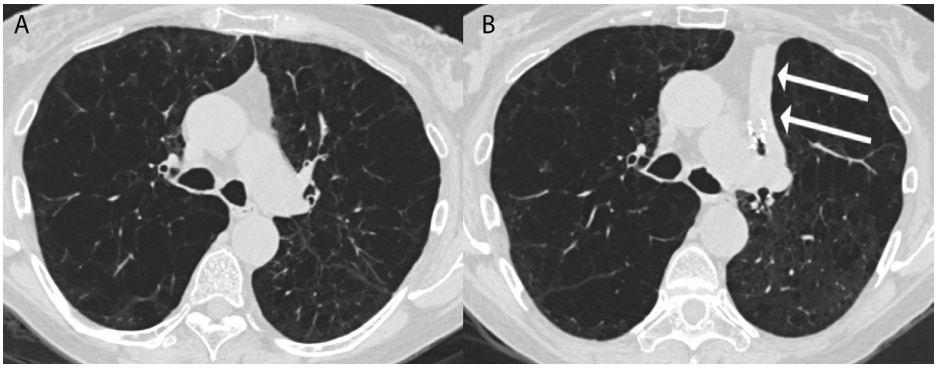

Figure 1: Two images of a chest high resolution CT-scan pre (Panel A) and 6 months post (Panel B) endobronchial valve treatment showing a complete atelectasis of the left upper lobe (white arrows).

METHODS

Study design

We retrospectively analysed data from 2 large clinical trials investigating endobronchial valve treatment: The "STELVIO trial" (Netherlands Trial Register number NTR2876(1)) and the "VENT trial" (NCT00129584(8)). The STELVIO and VENT trial were approved by the ethics committees of all participating hospitals and all patients provided informed consent.

In total 68 patients participated in the STELVIO trial and 321 patients participated in the VENT trial. Patients were included in our analyses when they both had an HRCT at baseline and 6 months follow-up after EBV treatment.

Measurements

Patients in both trials underwent HRCT scans at baseline and 6 months after the treatment. TLVR was calculated using quantitative HRCT analysis.

In the "STELVIO trial" post-hoc computerized quantifications using Thirona Lung Quantification (version 15.01) (11) were performed on the data set to determine the amount of TLVR (figure 2). Spirometry and body plethysmography (MasterScreen™; VIASYS, Höchberg, Germany) at baseline and 6 months follow-up were performed according to the American Thoracic Society/European Respiratory Society guidelines (12).

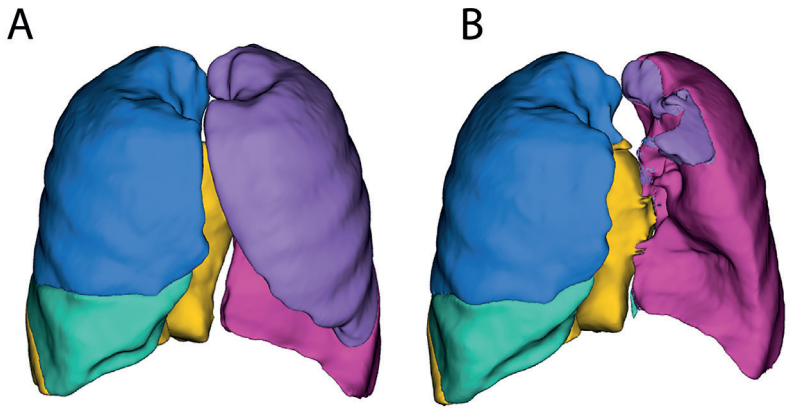

Figure 2: Three-dimensional reconstruction images of a chest high resolution CT-scan pre (plot A) and post (plot B) endobronchial valve treatment, showing a complete atelectasis of the left upper lobe which was associated with a TLVR of -1986ml, FEV_1 increase of 260ml and RV decrease of 1.36L, 6 months after endobronchial valve treatment.

In the "VENT trial", TLVR was measured by the study radiology core laboratory at the David Geffen School of Medicine (UCLA) through quantitative image analysis (MedQIA). Spirometry was performed based on the standardization of spirometry update by the American Thoracic Society (13) and body plethysmography was performed based on the American Association of Respiratory Care (AARC) clinical practice guideline (14) .

At baseline and at 6 months follow-up, patients in both trials were administered the full version of the St. George's Respiratory Questionnaire, a quality of life questionnaire with scores ranging from 0 to 100, with higher scores indicating worse quality of life (15).

MID calculation

To determine the MID, an anchor-based approach was used. The anchor-based method uses external indicators whose clinical validity is established and with a demonstrated MID in the target population (16). For the anchor-based method, we considered forced expiratory volume in 1 second (FEV_1) (MID 100ml (17)), residual volume (RV) (MID 430ml (18)), 6 minute walk distance (6MWD) (MID 26m (19)) and the St. George's Respiratory Questionnaire (SGRQ) (MID 8 Units (20)) as anchors.

The final MID was calculated using the average of the anchor-based MID's.

Data Analysis

The absolute and relative changes from baseline to 6 months follow-up were calculated. For the anchor-based method, Pearson correlation coefficients were calculated. In line with our previous studies we considered a Pearson correlation coefficient of $r \geq 0.4$ to indicate a sufficiently strong association (18,20). Linear regression analyses were performed with change in TLVR as dependent variable and change in anchor score as independent variable. The MID's of the anchors were then entered into the equations derived from the linear regression analyses. Afterwards, the MID could be calculated from the established equation. $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 22 (IBM, New York, NY, USA).

RESULTS

Seventeen patients in the "STELVIO trial"(1) and 54 patients in the "VENT trial" (8) did not perform an HRCT scan at 6 months follow-up and consequently 318 patients could be included in the analyses. Reasons for not completing the 6 months follow-up were amongst others: ineligibility for treatment, patient decline for follow-up and EBV removal due to adverse events.

Patient characteristics at baseline and change in outcome parameters at 6 months follow-up are shown in table 1.

Table 1: Patient characteristics at baseline and change scores between baseline and 6 months follow-up (Data are presented as mean ± standard deviation)

	Baseline	Δ at 6 months from baseline
n	318	
Female/Male	146/172	
Age (years)	64.2±7.1	
BMI (kg/m2)	24.9±3.86	
Packyears	58±30	
TLV (ml)	1807.3±514.2	-463.5±696.2
FEV_1 (ml)	861.9±264.9	53.4±171.8
RV (liter)	4.70±1.14	-0.20±0.95
SGRQ Total score (units)	52.2±13.0	-4.3±13.9

Δ=change between baseline and follow-up. BMI: body mass index; TLV: Target Lobar Volume; FEV_1: forced expiratory volume in 1 second; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire.

The Pearson correlation coefficient of TLVR with 6MWD was 0.32. This correlation coefficient did not meet the commonly accepted 0.40 correlation coefficient threshold and could therefore not be included as anchor in the MID calculation. The correlation coefficients and the MID calculations of the anchors are shown in table 2.

Scatterplots of correlations of TLVR versus FEV_1, RV and SGRQ at 6 months follow-up are shown in figure 3.

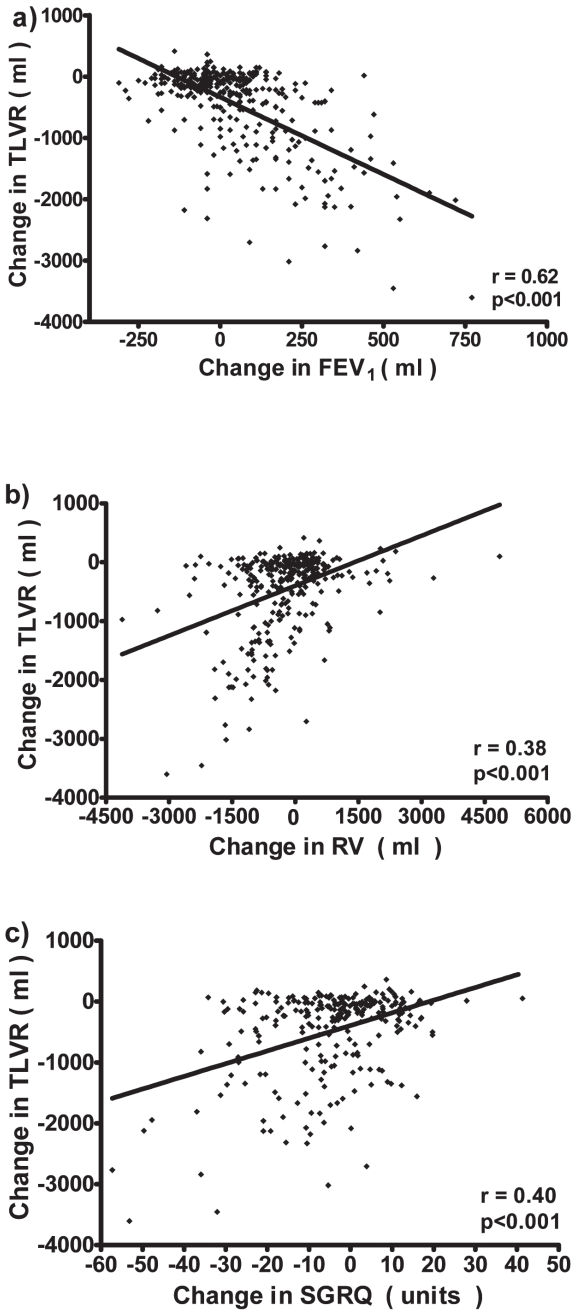

Figure 3: Scatterplots and Pearson correlation coefficients of forced expiratory volume in 1 second (FEV_1), residual volume (RV) and St. George's Respiratory Questionnaire (SGRQ) versus Target Lobar Volume Reduction (TLVR) at 6 months follow-up.

We calculated a TLVR MID of each anchor at 6 months follow-up: FEV_1 –587ml (relative MID –25.2%), RV –534ml (relative MID –21.3%) and SGRQ -560ml (relative MID -20.6%). Our combined MID (average of the 3 anchor-based MID's) was –563ml (relative –22.4%) at 6 months follow-up.

Table 2: Minimal important differences for TLVR

	Absolute TLVR MID at 6 months	Relative TLVR MID at 6 months
Anchor:		
FEV_1	-587ml (r: 0.62)*	-25.2% (r: 0.59)*
RV	-534ml (r: 0.38)*	-21.3% (r: 0.30)*
SGRQ	-560ml (r: 0.40)*	-20.6% (r: 0.26)*
Combined:	-563ml	-22.4%

TLVR: target lobar volume reduction; MID: minimal important difference; FEV_1: forced expiratory volume in 1 second; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; r: Pearson correlation coefficients. *) $P<0.001$

DISCUSSION

We have calculated for the first time a MID for TLVR in patients with severe emphysema. At 6 months follow-up after bronchoscopic lung volume reduction treatment using endobronchial valves the MID was –563ml and the relative MID was –22.4%. Our findings differ significantly from the currently accepted, expert opinion based, MID of 350ml.

The MID that we established was approximately 50% higher than the currently accepted cut-off value for TLVR of -350ml. Real data as basis for an MID for TLVR has never been published before and the cut-off value that is frequently used in the literature is based on expert opinion agreement. Based on our clinical experiences we hypothesized that the MID should be above the currently accepted 350ml threshold (7,10).

A possible contribution to this discrepancy is that the previous estimate of the MID was probably based on pulmonary function testing outcomes, underestimating the size of lung volume reduction due to the redistribution of lung volume from the target to the ipsilateral and contralateral lobes (21), leading to higher necessary HRCT TLVR values, when compared to pulmonary function generated values.

All included patients underwent BLVR using EBV. The question rises whether MID's based on anchor techniques can be used across different interventions as several processes may underlie the observed effects of interventions (22). Possibly, MID determination in patients who undergo lung volume reduction surgery or other bronchoscopic treatment modalities such as lung volume reduction coils, airway sealants or thermal vapor ablation could provide different MID results (23–26). Further research is required to assess the influence of different bronchoscopic treatment options on the TLVR MID calculation.

In this study we focused on the volume reduction of the target lobe and did not take into consideration for example the ipsi- or contralateral lobes. The ipsi- and contralateral lobes could expand after treatment. It is also possible that the character of the remaining lobe is of importance, for example emphysematous residual lung may offset the degree of lobar collapse. This might be investigated in future research.

There are different methods for the calculation of MID's, for example anchor-based methods which are patient oriented and distribution-based methods which focus on distribution of outcomes. There is no consensus on the best methodology. One of the recommendations in the literature is that the MID should be based primarily on relevant patient-based and clinical anchors (16). Therefore, we used the anchor-based method in this study. For the anchor-based method the choice of anchors can influence MID outcomes, therefore it is important to carefully select these anchors. One of the requirements for a good anchor is an high enough association between the anchor and the outcome variable (27). Despite the lower than 0.4 (0.38) Pearson correlation coefficient of the change in RV versus TLVR, the consistency of MID outcomes and our large sample size support the validity of our findings. Secondly, the anchor should be established in a comparable patient population. The anchors used in this study, with exception of the FEV_1 anchor, were all established in patients who underwent BLVR to treat severe emphysema. Other studies determining MID's included distribution-based methods as well (28,29). However a study by Turner *et al.* stated that the lack of consistency across distribution-based measures suggests that these approaches should act only as temporary substitutes, pending availability of empirically established anchor-based MID values (30). Terwee *et al.* even argue that distribution-based methods should not be used at all because they assess minimal detectable change, rather than minimal important change (31).

A limitation of this study is that patients from 2 different BLVR trials were included. For example, the VENT trial (8) included patients with heterogeneous emphysema whereas the STELVIO trial (1) included patients with both heterogeneous and homogeneous emphysema and excluded patients with measured collateral ventilation. Furthermore, different lung function protocols were used in both spirometry as well as body plethysmography. However, patients underwent the same treatment and we were able to include a large number of patients compared to other studies determining MID's. Furthermore, different volumetric quantification software analysis of the target lobes was performed in the 2 studies. Recent research suggests that the results from different software programs cannot always be considered interchangeable, however for longitudinal emphysema monitoring it was suggested that the scanning protocol and quantification software needs to be kept constant (32). In both studies used in our analysis, HRCT's were performed following the same scanning protocol and with the same software programs at baseline and 6 months follow-up.

In conclusion, this study is the first to establish an MID for TLVR measured on HRCT scan in patients with severe emphysema. This value can be useful for both interpreting the results from trials and clinical practice, as well as for designing future studies on lung volume reduction investigating BLVR treatments.

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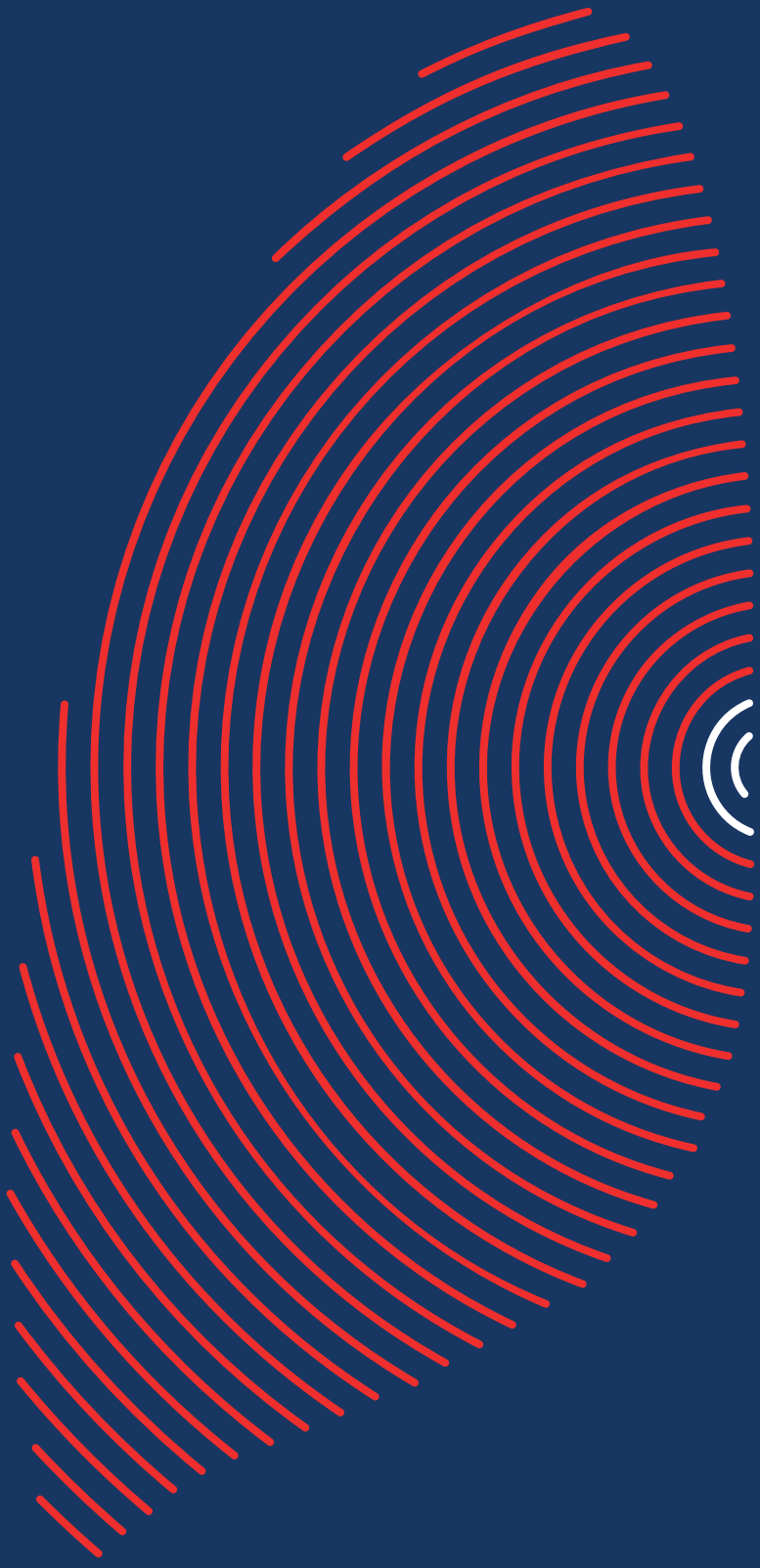

CHAPTER 11

Summary, discussion and future perspectives

SUMMARY

Bronchoscopic lung volume reduction (BLVR) is a treatment for patients with severe emphysema, aimed at reducing lung hyperinflation. It can be performed using different approaches, of which endobronchial valves and lung volume reduction coils are the most extensively investigated.

The goal of this thesis was to further advance the BLVR treatment by improving both the patient selection as well as the assessment of patient response after treatment. The results of the studies included in this thesis are summarized below.

Lung volume reduction coil treatment
In **chapter 2** we reviewed the available evidence on the efficacy and safety of treatment with lung volume reduction coils in patients with severe emphysema, a treatment especially suitable for patients who are ineligible for endobronchial valve therapy (1). The three randomized controlled clinical trials investigating the treatment with lung volume reduction coils that were published so far, demonstrated significant improvement of pulmonary function outcomes and quality of life in patients with severe hyperinflation (2–4). This benefit comes with a price of coil treatment induced complications, which are mainly inflammatory in origin: COPD exacerbations, pneumonia and coil associated opacity (1).

Patient selection for bronchoscopic lung volume reduction
In **chapter 3** we present the results of a large retrospective analysis of patients who were referred to our hospital to be evaluated for BLVR treatment. The aims of the study were twofold. Our first aim was to investigate which proportion of referred patients was actually selected for BLVR treatment, our secondary aim to identify differences in characteristics and survival between patients that were and were not selected for BLVR. In total, 1500 patients were included (mean age 62 years, 50% female and forced expiratory volume in 1 second (FEV_1) 33% of predicted). From this group only 19% was selected for BLVR treatment. Patients that were selected for BLVR lived significantly longer than the group of patients that was not selected for BLVR (median 3060 versus 2079 days, $P<0.001$). We found that only a small proportion of patients that is referred for BLVR treatment is eligible for a BLVR treatment, suggesting a large need for the development of new therapies for the group of patients that is currently not eligible for interventions. Furthermore, our data suggest that selection for BLVR treatment is associated with a significant survival benefit.

In **chapter 4** we analysed differences in body plethysmography outcomes between patients referred for BLVR to our hospital and their referring hospitals. We observed a significantly lower (median 310ml difference) residual volume in our hospital, compared to the total of 62 referring hospitals (5). Overestimation of residual volume can lead to unnecessary referrals for BLVR and when ignored, potential treatment failures. To prevent the overestimation of residual volume, it is important that body plethysmography measurements are accurately performed, preferably using the unlinked method in patients with severe emphysema. During the unlinked method, the inspiratory capacity measurement is performed directly after the intrathoracic gas volume manoeuver and for the calculation of residual volume, the maximum vital capacity measured during spirometry is used.

Chapter 5 describes the validation of a new functional assessment tool, designed to improve target lobe selection for treatment with endobronchial valves (6). We demonstrated that the bronchoscopic measurement of lobar oxygen uptake is feasible to perform in patients with severe emphysema and that a lower oxygen uptake capacity was significantly associated with higher lobar emphysematous destruction and lower arterial and venous vascular volume of the target lobes. These findings suggest that this approach, allowing for the quantification of oxygen uptake capacity at a lobar level, can support the identification of a treatment target for lung volume reduction treatment with endobronchial valves. However, more research is required in order to further validate this approach.

In both **chapter 6** and **chapter 7**, we investigated the effect of two different anesthesia techniques, procedural sedation and general anesthesia, on the bronchoscopic measurement of interlobar collateral ventilation (Chartis measurement). In **chapter 6** we performed a retrospective analysis in which we analysed all Chartis measurements which were performed in our hospital between October 2010 and December 2017. We included 250 patients with emphysema (median FEV_1 26% of predicted) and in total 746 Chartis readings were analysed. Performing Chartis measurement under general anesthesia was significantly faster and required less measurements when compared to procedural sedation, with no difference in target lobe volume reduction after treatment (7). In order to validate these findings, we performed a prospective trial comparing both anesthesia techniques. This study is presented in **chapter 7**, in which we prospectively compared Chartis measurement under procedural sedation versus general anesthesia. In this study, we confirmed the results of our retrospective analysis and found that Chartis measurement under

general anesthesia is faster and more feasible to perform compared to procedural sedation, without affecting measurement outcomes (8).

In **chapter 8**, we discuss a technical solution for Chartis measurement of the right major fissure that is complicated by the no flow phenomenon. The no flow phenomenon, is a sudden cessation of flow is observed during Chartis measurement, caused by dynamic expiratory airway collapse and leads to an unreliable measurement (9). If this phenomenon occurs in the right lower lobe, when measuring collateral flow over the right major fissure, the entrance to the right middle lobe should be occluded and the Chartis balloon should be placed in the right upper lobe. In this study, we present a case series of 15 patients (median FEV_1 24% of predicted) in which we demonstrated that temporary occlusion of the right middle lobe using a blocking device is feasible and that in this way a reliable Chartis measurement could be performed in all patients.

Assessment of response after treatment

In **chapter 9**, we established a new minimal important difference for the St. George's Respiratory Questionnaire (SGRQ) in patients with severe chronic obstructive pulmonary disease (COPD) who were selected for BLVR (10). We used both anchor- and distribution-based methods to define the minimal important difference. We included 115 severe COPD patients (mean FEV_1 26% of predicted, SGRQ score 62 units) who participated in seven different BLVR clinical trials. We proposed a minimal important difference of -8.3 SGRQ units at 1 month and -7.1 units at 6 months after treatment (11).

In **chapter 10**, we established a new minimal important difference for target lobe volume reduction after endobronchial valve treatment. We included 318 patients (mean FEV_1 0.9l and target lobe volume 1807ml) from two BLVR clinical trials. Using an anchor-based approach, we established an MID of -563ml at 6 months after endobronchial valve treatment in patients with severe emphysema.

The minimal important differences established in **chapter 9 and 10**, can be useful for both interpreting the results from clinical trials and regular practice, as well as for designing future studies on bronchoscopic lung volume reduction.

General discussion & future perspectives

Lung volume reduction coil treatment

The treatment with lung volume reduction coils can be considered in patients with emphysema, significant hyperinflation (RV >200% of predicted), who are not eligible for endobronchial valve treatment, but it remains under clinical investigation (12,13). A fourth, large prospective multicentre randomized controlled clinical trial comparing outcomes between lung volume reduction coils and a control group is underway to confirm the efficacy of this treatment (Clinicaltrials.gov: NCT03360396). In addition, a study investigating the effect of lung volume reduction on the lung microbiome is being performed (NCT03010566). Since only a small proportion of patients is eligible for endobronchial valve treatment, there is a clear need for alternative lung volume reduction techniques such as lung volume reduction coils. Future research should provide more insight in the exact mechanism of action, identify predictors of response, assess the durability of treatment benefit, investigate long term cost-effectiveness and potentially focus on new generation coil designs.

Patient selection

It is essential to carefully select patients for BLVR treatment, in order to achieve both safe and beneficial results. For example, interlobar collateral ventilation should be absent in order to achieve lobar atelectasis, and the treatment of patients with pleural adhesions increases the chance of pneumothorax after endobronchial valve treatment (14). Unfortunately, only a small proportion of patients that is referred for BLVR is considered eligible for these treatments. Therefore, new therapies should be developed for the population of patients with severe COPD that are currently considered ineligible for these interventions and who are unable to achieve satisfactory symptom control using regular medical therapy. In particular, for the treatment of patients with the severe chronic bronchitis phenotype of COPD, very limited treatment options are available. A new interventional therapy under development for chronic bronchitis is endobronchial treatment with liquid nitrogen cryospray, which is aimed at inducing an airway tissue healing effect by destroying hyperplastic goblet cells and excess submucous glands. However, until now, only the results from the first safety studies have been published and extensive research is required to investigate both the efficacy and safety profile of this treatment (15). Other novel experimental therapies include steam vapor ablation, which induces a reduction of lung volume by delivering water vapor, biological lung volume reduction, which uses a synthetic polymer in order to reduce lung volume and targeted lung denervation in which parasympathic pulmonary nerves are disrupted to decrease airway resistance and hypersecretion of mucus (16–18).

Next to the development of new interventions, research is being performed aimed at increasing the proportion of patients eligible for currently available interventions. The ability to restore interlobar fissure integrity could potentially increase the number of patients eligible for endobronchial valve treatment. The "MIND THE GAP trial" (Dutch Trial Register: NTR5007) is designed to investigate the feasibility of injecting autologous blood or synthetic polymer into the interlobar collateral ventilation channels, to restore the integrity of the fissure. Another approach is proposed by Majid *et al.*, who combined minimally invasive video assisted thoracic surgery (VATS), which allows for surgical stapling of the incomplete fissure, with the placement of endobronchial valves (19). In addition to the development of new therapies and efforts to increase the number of patients eligible for these treatments, the current first generation devices and delivery catheters of endobronchial valves and lung volume reduction coils could be evaluated and improved in new generations in order to provide easier handling, better biocompatibility, predictability of response, and potentially better functional outcomes.

Lung volume reduction surgery is still a valid treatment option in patients where a bronchoscopic approach is not an option, in patients with a predominantly paraseptal distribution of emphysema and in patients who have demonstrated significant initial effect after bronchoscopic treatment but where the effect was lost due to local complications or displacement of the valves (20). Between 2000 and 2010, the number of lung volume reduction surgeries in the United States decreased significantly, a trend probably affected by the results of the NETT trial by Fishman *et al.*, who found significant benefits of this treatment but at the cost of increased short term mortality and morbidity (21,22). However, between 2007 and 2013 the number of lung volume reduction surgeries started to increase again, possibly because of improved surgical techniques and strict patient selection resulting in better outcomes (23,24). A randomized controlled study, comparing lung volume reduction surgery and endobronchial valve treatment (CELEB trial; International Standard Randomized Controlled Trial Number (ISRCTN:19684749)) is currently being performed in the United Kingdom. We expect that the further implementation of BLVR techniques and new insights in patient selection for these treatments, will further increase the number of lung volume reduction surgeries and that bronchoscopic and surgical lung volume reduction techniques can co-exist (20).

Chartis measurement of interlobar collateral ventilation was originally validated under procedural sedation, in non-ventilated patients (25). Chartis measurement in patients who receive procedural sedation can be challenging for the physician performing this measurement because of issues with coughing, mucus and difficulties to maintain the right level of sedation (7). Arguments against Chartis measurement under general anesthesia could be the more extensive use of resources, the need for intubation and mechanical ventilation and the theoretical argument that ventilating patients using positive pressure might open collateral channels and consequently lead to false positive Chartis outcomes. However, no relevant difference in collateral ventilation outcome was observed in our prospective study between the two anesthesia techniques (8).

The 2019 expert recommendation guidelines for endobronchial valve treatment included the findings of our retrospective study and advised to perform Chartis measurement under general anesthesia (12). We confirmed the findings from our retrospective study in our prospective trial and we therefore advise to perform Chartis measurement under general anesthesia, preferably in the same session as the placement of the endobronchial valves (7,8). Performing both Chartis measurement and the placement of endobronchial valves in one procedure under general anesthesia is beneficial for the patient, as some hospitals perform separate procedures in which Chartis measurement is performed under procedural sedation, and these extra procedures can thus be avoided. There is no consensus yet in the literature on whether Chartis measurement can be replaced by quantitative CT analysis of fissure integrity in the future (26,27). Future research will have to clarify whether quantitative CT analysis is a strong enough independent predictor of collateral ventilation status or that bronchoscopic measurement remains indicated, perhaps in selected groups. In our opinion, Chartis measurement should be performed in every patient, as it is feasible to perform under general anesthesia and minimizes the chance of inappropriate endobronchial valve treatment in patients with positive interlobar collateral ventilation status, and subsequent patient disappointment.

While not the primary aim of the study, the results of our prospective study on the effect of anesthesia techniques on the feasibility and outcomes of Chartis measurement also provided insight in the occurrence of perioperative complications in patients with very severe emphysema (8). Based on this study and our clinical experience with our regular treatment program (BREATH-NL), we expect that the perioperative complication rate in patients with severe emphysema might be lower

than is currently anticipated, provided that general anesthesia is administered under strictly controlled circumstances such as: the presence of an experienced anesthesiologist, patients with a stable disease state and adapted ventilator settings. We suggest to perform a study investigating this possibility, as the outcomes of such a study might affect a large population of patients with severe emphysema who are now considered ineligible for different surgical interventions under general anesthesia.

Selecting the most suitable target lobe for endobronchial valve treatment can sometimes be a challenging task. Target lobe selection is based on several characteristics: the degree of emphysema destruction, absence of collateral ventilation, lobar volume of the target lobe and ipsilateral lobe, heterogeneity between both lobes, low lobar perfusion assessed using perfusion scintigraphy and absence of pleural adhesions (28–30). Selection of the target lobe for endobronchial valve treatment is currently mainly based on indirect imaging techniques. Previous research by Freitag *et al.* demonstrated the use of bronchoscopic capnometry and oximetry curves, to aid in target lobe selection (31). We investigated a more direct approach to assess lobar function: assessment of lobar oxygen uptake capacity, which can provide insight in the functional capacity of individual lobes. The benefit of this measurement is that it provides real time information about lobar function during bronchoscopy and could even be integrated in the new generation of Chartis measurement systems (6). We recommend that in the future, integrated collateral ventilation and oxygen uptake capacity measurement of individual lobes will be used in the selection of potential target lobes for endobronchial valve treatment.

Assessment of response after treatment

The second aim of our thesis was to improve the assessment of response after BLVR treatment. We have established new minimal important differences for both the SGRQ and for target lobe volume reduction after endobronchial valve treatment (11,30).

Our newly established minimal important difference for target lobe volume reduction, could prove to be a valuable addition to the field, as target lobe volume reduction is one of the most frequently used outcome measures in studies investigating endobronchial valves. However, while the reduction in volume of the target lobe is essential to the treatment, it must be kept in mind that compensatory inflation of the ipsilateral lobe can occur.

Therefore, the reduction in total lung volume might be more informative than solely the change in volume of the target lobe. In addition, in order to evaluate changes adjusted for high or low baseline scores, disease severity adjusted minimal important differences should be introduced (32). For example, while the minimal important difference for the SGRQ was established previously at -4 SGRQ units, our minimal important difference of -8.3 units at 1 month and -7.1 units at 6 months after treatment, might be more appropriate to use in patients with severe COPD (11,33). The concept of minimal important differences in general is still in development and some questions regarding the applicability and interpretation of minimal important differences remain unanswered. No consensus exists on whether minimal important differences should be assessed in a treatment- and disease severity-specific manner (34).

Most clinical trials investigating BLVR techniques already incorporated the proportion of patients achieving the minimal important differences after treatment: we encourage the inclusion of the proportion of patients achieving minimal important differences (responder rates) in future BLVR research and the respiratory field in general.

The active engagement of patients when major health care decisions must be made is considered a cornerstone of patient centered care (35). A previous study found that the majority of patients with severe emphysema prefer a procedure comparable to endobronchial valve treatment over their current medical management (36). In our hospital, the balance between potential side effects and benefits is discussed with every potential candidate for BLVR treatment. Other examples of patient centered care might include the evaluation of patient reported goals, for example the ability to independently take a shower or take care of grandchildren, which might perhaps better reflect relevant improvement for the patient than the use of more traditional patient reported outcome measures (37).

Endobronchial valve treatment has been associated with prolonged survival, provided that successful lobar atelectasis is achieved (38–40). For lung volume reduction coil treatment, structural survival data is not yet available. Therefore, more research is needed to provide insight in long term survival after both endobronchial valve treatment and lung volume reduction coil treatment.

Conclusions

In conclusion, with the studies in this thesis, we have been able to obtain further insight in and contributed to the advancement of BLVR treatment in patients with severe emphysema. The studies described in this thesis may help the clinician in selecting the right patients for BLVR treatments and may provide more insight in the assessment and identification of patients with a meaningful clinical improvement of response after BLVR treatment.

The main results

I: Treatment with lung volume reduction coils as alternative for patients ineligible for endobronchial valves, results in significant improvement of pulmonary function outcomes and quality of life in patients with severe hyperinflation.
II: Only a small proportion of the patients referred for BLVR is eligible for treatment; when selected for treatment, significant survival benefit can be expected.
III: Measurement of lobar oxygen uptake can help to identify the least functional lobe and could be used as additional tool for endobronchial valve treatment target lobe selection.
IV: Chartis measurement is faster and more feasible to perform under general anesthesia compared to procedural sedation, without affecting measurement outcomes.
V: The minimal important differences for the St. George's Respiratory Questionnaire and target lobe volume reduction are respectively -7.1 units and -563ml at 6 months after treatment.

The main future perspectives

Future research should be performed in order to:

I: Develop new therapies for the large population of patients with severe COPD that are currently considered ineligible for endobronchial interventions.
II: Increase the number of patients eligible for endobronchial valve treatment, for example by restoring interlobar fissure integrity.
III: Improve measurement of lobar function in order to guide target lobe selection for endobronchial valve treatment.
IV: Develop further insight in the applicability and interpretation of minimal important differences.
V: Provide insight in long term survival after bronchoscopic lung volume reduction

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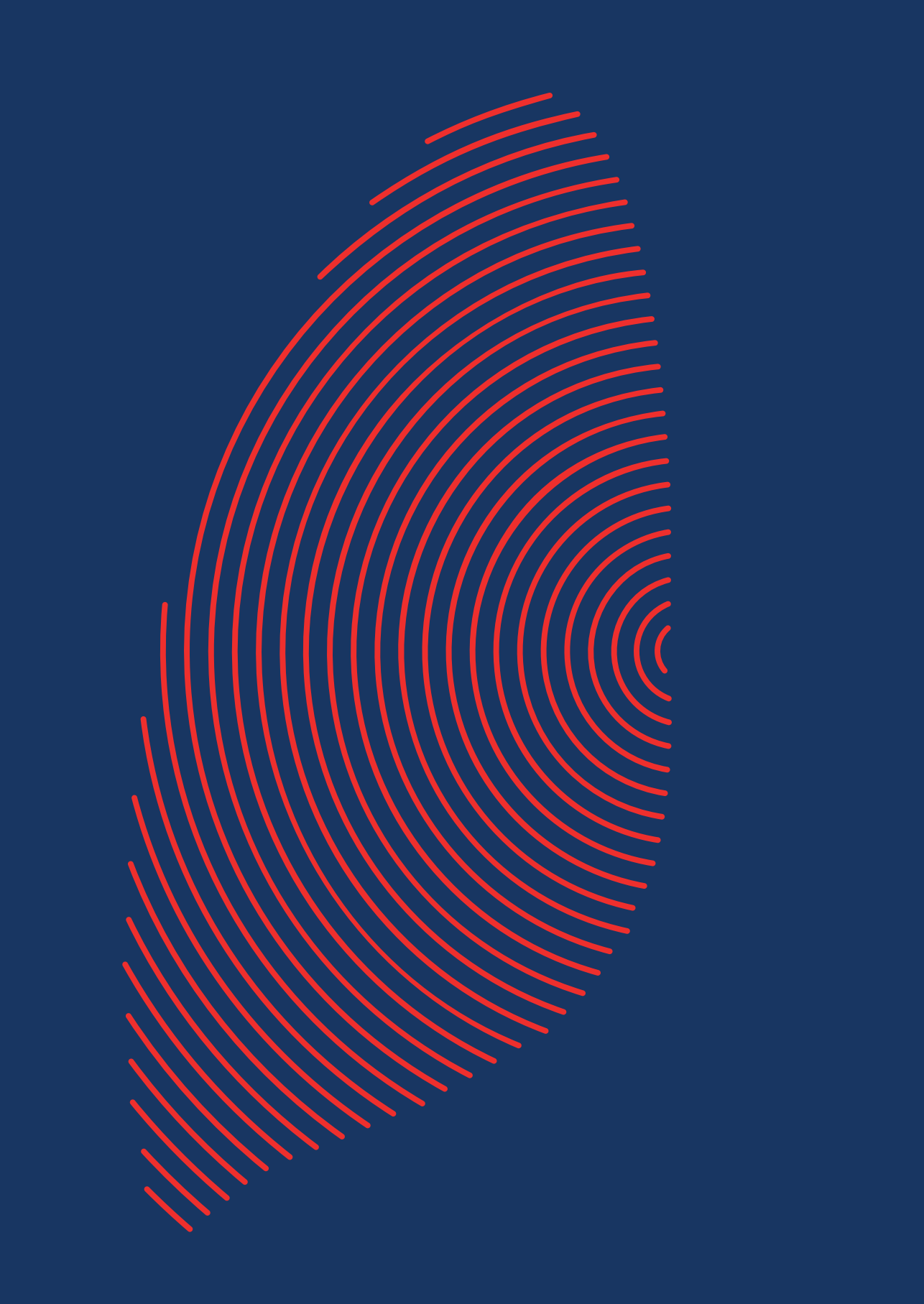

APPENDICES

Nederlandse Samenvatting

Dankwoord

Curriculum Vitae

NEDERLANDSE SAMENVATTING

COPD

Chronische obstructieve longziekte (COPD: "Chronic obstructive pulmonary disease") is een chronische, progressieve longaandoening die wordt gekenmerkt door een vernauwing van de luchtwegen en verval van longblaasjes. Symptomen van COPD zijn onder andere kortademigheid, chronisch hoesten, toegenomen slijmproductie en een verhoogde vatbaarheid voor luchtweginfecties (1). Wereldwijd overleden 3 miljoen mensen aan deze aandoening in 2016, daarmee is het de op twee na meest voorkomende doodsoorzaak (2). In Nederland hebben ongeveer 600,000 mensen COPD (3). De belangrijkste risicofactor voor het ontwikkelen van COPD is roken, maar ook beroepsmatige blootstelling aan stofdeeltjes, luchtvervuiling, blootstelling aan verbrandde biomassa en genetische aanleg kunnen bijdragen aan het ontstaan van deze aandoening. COPD kan worden onderverdeeld in verschillende fenotypen, waarvan luchtwegziekte (bronchitis) en destructie van de longblaasjes (emfyseem) de belangrijkste zijn (1).

Behandeling van COPD

COPD is een ongeneeslijke aandoening. De beschikbare behandelingen voor COPD zijn gericht op verlichting van symptomen en het vertragen van progressie. Voorbeelden van deze behandelingen zijn: stoppen met roken, luchtwegverwijdende en ontstekingsremmende medicatie, zuurstoftherapie, longrevalidatie, niet-invasieve beademing en chirurgische interventies zoals longtransplantatie en longvolumereductie chirurgie.

Naast de bovengenoemde opties zijn bronchoscopische longvolumereductie behandelingen in opkomst. Deze behandelingen voor patiënten met het ernstig emfyseem fenotype van COPD, zijn gericht op het verminderen van "hyperinflatie" van de long. Hyperinflatie houdt in dat er, als gevolg van de COPD, een groter dan normale hoeveelheid lucht in de longen aanwezig is, die niet of niet snel genoeg kan worden uitgeademd. Deze hyperinflatie zorgt voor een toename van de kortademigheid en beperkt het inspanningsvermogen van de patiënt. Er bestaan verschillende vormen van bronchoscopische longvolumereductie, waarvan de behandelingen met éénrichtingsventielen en longvolumereductie coils het meest uitgebreid onderzocht zijn (4). Andere methoden van bronchoscopische longvolumereductie, zoals behandeling met stoom of synthetische polymeren zijn nog in ontwikkeling (5,6).

Behandeling met éénrichtingsventielen

Bij de behandeling met éénrichtingsventielen wordt de ingang van een longkwab afgesloten met één of meerdere éénrichtingsventielen. Door deze éénrichtingsventielen kan er wel lucht uit deze longkwab stromen maar er niet meer terug in. Een longkwab waar geen lucht meer inkomt valt uiteindelijk samen, en dat is precies het doel van de behandeling met éénrichtingsventielen. Een voorwaarde voor effectief samenvallen is dat de scheiding (fissuur) tussen de behandelde en naastliggende longkwabben intact is en er dus geen luchtstroom (collaterale ventilatie) bestaat tussen deze longkwabben, waardoor de behandelde longkwab dus niet echt afgesloten is. Bij aanwezigheid van collaterale ventilatie zal de longkwab niet samenvallen na plaatsing van de éénrichtingsventielen en is de behandeling daarmee niet effectief (7).

Het is mogelijk om op basis van een CT-scan van de longen redelijk te voorspellen of er sprake is van collaterale ventilatie. Door middel van kwantitatieve CT analyse kan door software berekend worden of de fissuren tussen de 5 verschillende longkwabben intact zijn. Hoe intacter de fissuur is, hoe kleiner de kans op aanwezigheid van collaterale ventilatie (8).

Aanvullende informatie over collaterale ventilatie kan verkregen worden door middel van de "Chartis" meting. Tijdens de Chartis meting wordt de te behandelen longkwab afgesloten met een speciale ballonkatheter; hierna kan er gemeten worden hoeveel lucht er door de katheter uit de longkwab stroomt. Bij patiënten zonder collaterale ventilatie zal deze hoeveelheid lucht over de tijd geleidelijk afnemen omdat de longkwab leegloopt. Bij patiënten die wel collaterale ventilatie hebben zal deze hoeveelheid lucht constant blijven, er wordt dan immers nieuwe lucht aangevoerd vanuit de naastliggende longkwab naar de te meten longkwab (8).

Behandeling met longvolumereductie coils

Bij de behandeling met longvolumereductie coils worden speciale "coils" (spiralen), gemaakt van geheugenmetaal, met de bronchoscoop in de longen geplaatst. Deze coils krullen na plaatsing in de long op en zorgen voor het samentrekken van aangedaan longweefsel en daarmee de gewenste longvolumereductie. Deze behandeling kan ook worden uitgevoerd bij aanwezigheid van collaterale ventilatie tussen longkwabben en is dus een alternatief voor patiënten die niet in aanmerking komen voor behandeling met éénrichtingsventielen (9).

Doel van het proefschrift

Het doel van dit proefschrift was tweeledig: ten eerste wilden we de selectie van patiënten voor bronchoscopische longvolumereductie verbeteren en daarnaast wilden we de uitkomsten na bronchoscopische longvolumereductie beter kunnen evalueren en interpreteren. De belangrijkste resultaten van de onderzoeken in dit proefschrift zijn hier samengevat.

Behandeling met longvolumereductie coils

In **hoofdstuk 2** hebben we de beschikbare literatuur over effectiviteit en veiligheid van de behandeling met longvolumereductie coils voor patiënten met ernstig emfyseem onderzocht. Op dat moment waren er drie gerandomiseerde klinische studies gepubliceerd waarin deze behandeling werd onderzocht. Deze drie studies lieten allen significante verbeteringen zien in longfunctie en kwaliteit van leven (10–12). De complicaties die het vaakst werden gezien na deze behandeling waren COPD longaanvallen (exacerbaties), longontsteking en "coil associated opacity" (een lokale, niet infectieuze ontstekingsreactie rondom de coils) (9).

Patiënt selectie voor bronchoscopische longvolumereductie

In **hoofdstuk 3** presenteren we de resultaten van een studie waarin we patiënten hebben onderzocht die werden verwezen naar ons ziekenhuis, om te beoordelen of ze in aanmerking kwamen voor een bronchoscopische interventie. Het hoofddoel van deze studie was om te onderzoeken hoeveel procent van de patiënten die werden verwezen naar ons ziekenhuis, ook daadwerkelijk in aanmerking kwamen voor een behandeling. Daarnaast hebben we onderzocht of er verschillen waren in patiëntkarakteristieken en overleving tussen patiënten die wél of niet geselecteerd werden voor een behandeling. In totaal includeerden we 1500 patiënten (gemiddeld 62 jaar oud, 50% vrouw met een FEV_1 van 33% van voorspeld). Van de totale groep verwezen patiënten werd slechts 19% geselecteerd voor bronchoscopische longvolumereductie behandeling. De belangrijkste redenen waarom patiënten niet geselecteerd werden voor behandeling waren: de afwezigheid van een geschikte behandelkwab, een ongeschikt COPD fenotype (bijvoorbeeld chronische bronchitis) en onvoldoende hyperinflatie. Patiënten die werden geselecteerd leefden significant langer dan de groep patiënten die niet werd geselecteerd voor de behandeling (mediane overleving na verwijzing 3060 dagen versus 2079 dagen).

Onze conclusie was dat slechts een klein deel van de patiënten die verwezen worden voor een bronchoscopische longvolumereductie behandeling hier daadwerkelijk voor in aanmerking komt. Dit geeft aan dat het erg belangrijk is om nieuwe

behandelingen te ontwikkelen voor de grote groep patiënten die op dit moment nog niet in aanmerking komt voor bronchoscopische interventies. Daarnaast suggereert onze data dat bronchoscopische longvolumereductie behandeling is geassocieerd met een significante overlevingswinst.

In **hoofdstuk 4** hebben we verschillen in bodybox metingen vergeleken tussen ons ziekenhuis en de naar ons verwijzende ziekenhuizen, bij patiënten die waren verwezen voor een bronchoscopische behandeling. De bodybox meting is een methode om de totale inhoud van de longen en het residuaal volume te bepalen. Het residuaal volume is het volume lucht dat na een maximale uitademing in de longen achterblijft en is een maat voor de hoeveelheid hyperinflatie. In dit onderzoek constateerden we in ons ziekenhuis een significant lager residuaal volume dan in de verwijzende 62 ziekenhuizen (mediaan 310ml verschil). Aangezien alleen mensen met een hoog residuaal volume in aanmerking komen voor bronchoscopische longvolumereductie is dat een relevante bevinding: overschatting van het residuaal volume kan leiden tot onnodige verwijzingen en daarmee teleurstelling bij patiënten en onnodige zorgkosten. Om deze reden is het van belang dat de bodybox meting wordt uitgevoerd met specifieke aandacht voor de patiëntengroep met ernstig COPD. Een element hiervan is dat de longfunctie-analist die de meting uitvoert, ruim de tijd neemt om de patiënt volledig te laten uitademen tijdens de longfunctiemetingen: een uitdaging bij deze groep patiënten die problemen heeft met uitademen. Daarnaast heeft het de voorkeur dat de bodybox meting wordt uitgevoerd met de “unlinked” methode. Tijdens de unlinked methode wordt er voor het berekenen van de totale longcapaciteit, naast de gegevens van de bodybox meting, gebruik gemaakt van resultaten uit los uitgevoerd spirometrie onderzoek. Dit is in tegenstelling tot de “linked” methode waarin patiënten in de bodybox deze spirometrie metingen moeten uitvoeren. Deze “linked” combinatie van aansluitend een bodybox en spirometrie meting is uitdagend voor patiënten met ernstig COPD en zorgt daarmee voor een overschatting van het residuaal volume (13).

Hoofdstuk 5 beschrijft de validatie van een nieuwe meetmethode om de selectie van de behandelkwab voor éénrichtingsventielen te verbeteren. Tijdens deze meting wordt bepaald hoe goed een individuele longkwab zuurstof kan opnemen. De te meten longkwab wordt afgesloten middels een ballonkatheter, waarna wordt gemeten hoe snel de zuurstofconcentratie in de longkwab daalt. In deze studie laten we zien dat bronchoscopische meting van zuurstofopname-capaciteit van individuele longkwabben goed uitvoerbaar is. De belangrijkste bevinding van dit onderzoek was dat een lagere zuurstofopname-capaciteit gerelateerd was aan

zowel een hogere mate van destructie van het longweefsel als met lagere arteriële en veneuze vaatvolumes van deze potentieel te behandelen longkwabben. Deze resultaten suggereren dat deze nieuwe selectieve bronchoscopische meting van zuurstofopname-capaciteit kan bijdragen aan het identificeren van de juiste te behandelen longkwab voor éénrichtingsventielen. Nader onderzoek is noodzakelijk om deze meting verder te valideren, maar we verwachten dat in de toekomst de selectie van te behandelen longkwabben voor éénrichtingsventielen vaker gebaseerd zal zijn op deze meting van functionele status, in aanvulling op de huidige beeldvormingstechnieken (14).

In **hoofdstuk 6 en 7** hebben we het effect van twee typen anesthesie: sedatie ("roesje") versus algehele narcose vergeleken op de bronchoscopische meting van collaterale ventilatie tussen longkwabben (de Chartis meting). Deze meting is van groot belang voor de behandeling met éénrichtingsventielen. Bij patiënten waarbij collaterale ventilatie (luchtstroom) tussen de verschillende longkwabben aanwezig is, zal deze behandeling namelijk niet tot het gewenste resultaat leiden. De Chartis meting is oorspronkelijk gevalideerd bij patiënten onder sedatie, die spontaan ademden (niet beademd werden) (15). In de praktijk bleek het echter lastig om deze meting onder sedatie uit te voeren: vaak traden er problemen op door hoesten van de patiënt, wat het op de juiste plaats houden van de katheter tijdens de meting lastig maakte, of waren er problemen met het stabiel houden van de sedatie (16). Deze problemen vormden de aanleiding om in **hoofdstuk 6 en 7** uit te zoeken of er verschil was in Chartis uitkomsten tussen de meting onder sedatie of onder algehele narcose.

In **hoofdstuk 6** hebben we een retrospectieve analyse uitgevoerd van alle Chartis metingen die in ons ziekenhuis werden uitgevoerd tussen Oktober 2010 en December 2017. In deze studie includeerden we 250 patiënten met emfyseem en analyseerden we 746 Chartis metingen. Het uitvoeren van Chartis metingen onder algehele narcose ging sneller en er hoefden minder afzonderlijke metingen uitgevoerd te worden, vergeleken met het uitvoeren van de Chartis meting onder sedatie. Daarnaast vonden we geen verschil tussen de anesthesie technieken in de gewenste volume afname van de behandelde longkwabben (16). Om de resultaten uit hoofdstuk 6 te valideren hebben we een prospectieve studie opgezet om de anesthesie technieken te vergelijken. De resultaten van deze studie worden besproken in **hoofdstuk 7**. In deze studie werd de Chartis meting in elke patiënt uitgevoerd onder zowel sedatie als algehele narcose. Deze studie bevestigde de resultaten van onze retrospectieve studie: Chartis metingen onder algehele narcose

zijn sneller en makkelijker uit te voeren in vergelijking met Chartis meting onder sedatie, zonder dat dit negatieve invloed heeft op de uitkomsten van de meting (17).

In **hoofdstuk 8** bespreken we een oplossing voor Chartis meting van de rechter fissura major (de scheiding tussen de onder- en bovenkant van de rechter long) die gecompliceerd wordt door een "no flow" fenomeen in de rechteronderkwab. Tijdens het "no flow" fenomeen, stopt de flow tijdens Chartis abrupt, wat leidt tot een onbetrouwbare meting (18). De theorie is dat dit wordt veroorzaakt door het samenvallen van de kleinere luchtwegen tijdens de meting (18). Wanneer dit fenomeen optreedt in de linkeronderkwab kan er worden uitgeweken naar de linkerbovenkwab om de linker fissura major door te meten. In de rechterlong zijn er echter drie longkwabben en twee fissuren, daarom kan er bij een "no flow" fenomeen in de rechteronderkwab niet zomaar in de rechterbovenkwab worden gemeten. De aanwezigheid van de rechtermiddenkwab kan bij die benadering leiden tot een fout-positieve uitkomst van de meting (de Chartis meting geeft aan dat er sprake is van collaterale ventilatie maar dit is niet daadwerkelijk het geval). Om alsnog een betrouwbare Chartis meting van de rechter fissura major te verkrijgen, dient de rechter middenkwab tijdelijk afgesloten te worden met een 'blocking device'. Dit kan bijvoorbeeld met een "Watanabe spigot" of met een ballonkatheter. De Watanabe spigot is een siliconen plugje met een diameter van 7mm, die kan worden gebruikt om een luchtweg tijdelijk af te sluiten. Bij de ballon katheter kan een ballon, die zich aan het uiteinde van de katheter bevindt, worden opgeblazen tot een diameter tussen de 5 en 20mm. In deze studie presenteren we resultaten van 15 longvolumereductie patiënten waarin we laten zien dat tijdelijke afsluiting van de rechtermiddenkwab met de Watanabe spigot of ballon katheter goed uitvoerbaar is en resulteerde in een betrouwbare Chartis meting in alle patiënten.

Beoordelen van het behandeleffect

Na een bronchoscopische longvolumereductie behandeling wordt er uitgebreid geëvalueerd in hoeverre er verbetering is in kwaliteit van leven en klinische uitkomsten voor de patiënt. In wetenschappelijk onderzoek wordt door middel van statistische testen getoetst of een verschil statistisch significant is (niet op toeval gebaseerd). Bij klinische studies met grote aantallen patiënten wordt regelmatig een klein maar statistisch significant verschil gevonden. Dit statistisch significant verschil is echter niet altijd ook een klinisch relevant verschil voor de patiënt. Daarom wordt ook wel het minimaal klinisch relevant verschil gebruikt. Dit is een afkapwaarde voor een specifieke uitkomstvariabele die voor een individuele patiënt waarneembaar

is: elk verschil dat groter is dan deze afkapwaarde wordt beschouwd als klinisch relevant.

In **hoofdstuk 9**, hebben we een nieuw minimaal klinisch relevant verschil ("minimal inportant difference (MID)") berekend voor de kwaliteit van leven vragenlijst van het St. George ziekenhuis (SGRQ). De SGRQ vragenlijst wordt vaak gebruikt bij patiënten met COPD en meet de kwaliteit van leven van deze patiënten (19). Hoe hoger de score op deze vragenlijst, hoe slechter de kwaliteit van leven is. Er bestond al een MID voor de SGRQ, echter deze was niet gevalideerd voor patiënten met ernstig COPD (20). In onze studie hebben we 115 patiënten met ernstig COPD geïncludeerd (gemiddelde SGRQ score 62 punten) die deel hadden genomen aan 7 verschillende studies naar bronchoscopische longvolumereductie. We hebben een MID vastgesteld van -8.3 SGRQ punten op 1 maand en -7.1 punten op 6 maanden na behandeling. Deze was wezenlijk hoger dan de oude MID voor de SGRQ van -4 punten. Deze nieuwe MID's kunnen gebruikt worden voor de interpretatie van SGRQ uitkomsten in klinische studies en voor berekening van het minimum aantal patiënten dat nodig is om betrouwbare uitkomsten te verkrijgen in toekomstige studies naar interventies bij patiënten met ernstig COPD (21).

In **hoofdstuk 10**, hebben we de MID voor target lobe volume reduction (de gewenste afname van het volume van de behandelde longkwab) na behandeling met éénrichtingsventielen vastgesteld. Dit volume van longkwabben kan worden bepaald door middel van kwantitatieve CT analyse en is een belangrijke uitkomstmaat voor de behandeling met éénrichtingsventielen. Op het moment van uitvoeren van deze studie was er voor deze belangrijke uitkomst nog geen formele MID bepaald. We hebben 318 patiënten geïncludeerd (gemiddeld FEV_1 0.9 liter en volume van de te behandelen longkwab 1807ml) uit 2 studies waarin patiënten werden behandeld met éénrichtingsventielen. We hebben een MID vastgesteld van -563ml op 6 maanden na behandeling met éénrichtingsventielen: het volume van de behandelde longkwab moet dus minimaal afnemen met 563ml om een klinisch relevant effect te bereiken. Deze MID kan zeer bruikbaar zijn in de klinische praktijk, bij de interpretatie van toekomstige wetenschappelijke onderzoeken en is daarnaast ook van belang voor het opzetten van nieuwe studies naar longvolumereductie behandelingen (22).

Conclusie
Met de studies beschreven in dit proefschrift hebben we nieuwe inzichten verkregen in en bijgedragen aan de ontwikkeling van bronchoscopische longvolumereductie behandelingen bij patiënten met ernstig emfyseem. Deze studies bieden de clinicus handvaten om de juiste patiënten te selecteren voor bronchoscopische longvolumereductie behandelingen en bieden nieuwe inzichten in de beoordeling en identificatie van patiënten met een klinisch relevante verbetering na de bronchoscopische longvolumereductie behandeling.

DE BELANGRIJKSTE BEVINDINGEN

I: Behandeling met longvolumereductie coils, als alternatief voor patiënten die geen kandidaat zijn voor éénrichtingsventielen, resulteert in significante verbetering van longfunctie en kwaliteit van leven bij patiënten met ernstige hyperinflatie.

II: Slechts een kleine selectie van de patiënten die worden verwezen voor bronchoscopische longvolumereductie komt in aanmerking voor behandeling; in het geval van selectie voor behandeling kan een significante overlevingswinst worden verwacht.

III: Meting van zuurstofopnamecapaciteit per longkwab kan bijdragen aan identificatie van de minst functionele longkwab en zo gebruikt worden bij het selecteren van een behandelkwab voor éénrichtingsventielen.

IV: Chartis metingen zijn sneller en makkelijker uit te voeren onder algehele narcose in vergelijking met sedatie, zonder dat dit de uitkomsten van de meting en de behandeling beïnvloedt.

V: Het minimaal klinisch relevant verschil voor de vragenlijst van het St. George ziekenhuis is -7.1 punten 6 maanden na bronchoscopische longvolumereductie.

VI: Het minimaal klinisch relevant verschil voor target lobe volume reductie is -563ml 6 maanden na bronchoscopische longvolumereductie.

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Groningen, Januari 2020

Jorrit

CURRICULUM VITAE

Jorrit Ben Auke Welling werd geboren op 27 Juli 1992 in Nieuwegein (Utrecht), waarna hij opgroeide in Oosterhout (Noord-Brabant) en Heiloo (Noord-Holland).

Na het behalen van zijn gymnasiumdiploma in 2010 aan het Bonhoeffer College in Castricum, startte hij met de studie Economics and Business Economics aan de Rijksuniversiteit Groningen. Een jaar later, in September 2011, kon hij beginnen aan de studie Geneeskunde aan dezelfde universiteit. De eerste drie jaar van zijn studie was hij lid van roeivereniging "G.S.R. Aegir", actief bij de medische faculteitskroeg "Villa Volonté" en deed hij zijn eerste onderzoekservaringen op in het "Prometheus-team": een studenten-onderzoeksteam gericht op orgaandonatie en niertransplantatie.

In 2014 begon hij zijn wetenschappelijke stage bij het Bronchoscopisch Interventie Centrum van de afdeling Longziekten en Tuberculose in het Universitair Medisch Centrum Groningen (UMCG). Deze wetenschappelijke stage resulteerde in een eerste publicatie en een poster-presentatie op het American Thoracic Society congres in Denver.

Vervolgens werd hij aangenomen voor het MD/PhD programma, een verkort promotietraject waarin hij zijn co-schappen in respectievelijk het UMCG en de Isala Klinieken in Zwolle afwisselde met 2 jaar fulltime verrichten van wetenschappelijk onderzoek. Bij dit onderzoek werd hij begeleid door prof.dr. Dirk-Jan Slebos, prof.dr. Huib Kerstjens en dr. Jorine Hartman. Zijn semi-arts stage liep hij bij de afdelingen Longziekten en Intensive Care van het UMCG, waarna hij in December 2018 de studie Geneeskunde afrondde.

Na dit promotietraject start hij met de opleiding tot longarts. Vanaf Maart 2020 begint hij met de vooropleiding Interne Geneeskunde in het Martini Ziekenhuis te Groningen. Daarna zal hij de opleiding tot longarts voortzetten in het Universitair Medisch Centrum Groningen.