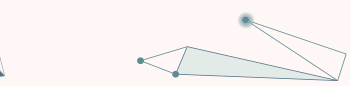
CHAPTER

13

Summary



SUMMARY

Bronchoscopic lung volume reduction offers a valuable additional therapeutic option for patients with severe COPD characterized by emphysema and substantial lung hyperinflation. One-way endobronchial valves and lung volume reduction coils are the most extensively studied bronchoscopic lung volume reduction approaches, although various other approaches have been studied over the past years and/or are currently under investigation. As of now, endobronchial valves are the only bronchoscopic lung volume reduction option that is available as a routine care option in the Netherlands.

The goal of this thesis was to broaden the knowledge of bronchoscopic lung volume reduction (BLVR). Specifically, we aimed to identify patient characteristics associated with positive outcomes and to deepen the insights into the airway granulation response following endobronchial valve treatment. Additionally, we explored if lung volume reduction coil treatment is a bronchoscopic lung volume reduction option that holds potential. A summary of the studies within this thesis is outlined below.

Anaesthetic management for BLVR procedures

In **chapter 2** we performed a retrospective study of 202 bronchoscopic lung volume reduction procedures performed in our hospital. The aim was to evaluate the anaesthetic management during these procedures, the number and type of anaesthesia-related adverse events, and to give some recommendations based on our findings. We found that most procedures are performed under general anaesthesia with endotracheal intubation. Hypotension was the most frequently encountered anaesthesia-related adverse event. Our study confirmed that general anaesthesia during bronchoscopic lung volume reduction procedures is well-tolerated by patients with severe COPD if sufficient time for complete expiration is allowed. Key considerations to achieve this are using a low respiratory rate (9 to 11 breaths/min), a low tidal volume (6 to 8 mL/kg), and a high inspiratory-to-expiratory ratio (around 1:3).

Hyperinflation assessment

In **chapter 3** we compared the reference values for residual volume derived from the European Community for Steel and Coal (ECSC) and the new Global Lung Function Initiative (GLI) reference equations. Standardized residual volume values, combined with the residual volume to total lung capacity ratio, are used to assess hyperinflation severity in potential bronchoscopic lung volume reduction candidates. Until the introduction of the GLI reference equations in 2021, the ECSC reference equations were widely used. We found that there are substantial differences between the residual volume reference values, where the GLI reference value is consistently lower for individuals with an average or below-average height (163cm for females and 177cm for males). Additionally, we established that a GLI-derived z-score of 2.9 or above is an accurate alternative for the ECSC-derived threshold of 175% of predicted that is frequently used as guidance to identify patients with sufficient hyperinflation to be considered for a bronchoscopic lung volume reduction treatment.

Predictors of response

In **chapter 4** we evaluated long-term survival after endobronchial valve treatment and the influence of treatment response on survival in a cohort of 428 patients. We observed a median survival time of 8.2 years after treatment. Patients identified as responders, based on their improvement in 6-minute walk distance or on the St. George's respiratory questionnaire, exhibited a survival benefit compared to nonresponders. The presence of a complete lobar atelectasis or response based on their improvements in pulmonary function outcomes were not associated with enhanced survival. Our findings suggest that, in the context of survival after endobronchial valve treatment, improvements in exercise capacity and quality of life are more significant than improvements in pulmonary function or the presence of a complete lobar atelectasis.

In **chapter 5** we evaluated the association between the heterogeneity index, a surrogate for emphysema distribution, and response to endobronchial valve treatment, using the data of 236 patients who received the treatment in our hospital. We showed that heterogeneity index does influence the magnitude of improvements in pulmonary function, exercise capacity, and quality of life. A higher index, meaning a more heterogeneous distribution of emphysema, is associated with more pronounced improvements. However, many patients with a more homogeneous distribution also experienced clinically meaningful improvements. Consequently, we argue against using emphysema distribution as a sole determinant for patient selection but emphasize that it should be considered within the broader context of all other patient selection criteria.

In **chapter 6** we performed a cluster analysis to identify responder and nonresponder groups after endobronchial valve treatment with the objective to evaluate the differences and similarities between them. Three clusters were identified: one nonresponder cluster and two responder clusters. Distinct differences in target lobe characteristics were observed between the nonresponder and the two responder clusters, without significant differences in pre-treatment pulmonary function or exercise capacity. The target lobe of the nonresponders exhibited less destruction and air trapping, combined with a higher perfusion and a more homogeneous emphysema distribution compared to the ipsilateral nontargeted lobe. On the other hand, differences between the responder clusters were associated with disease severity, considering parameters such as pulmonary function, exercise capacity, symptoms, and quality of life. These findings underscore the significance of quantitative CT scan analysis and the importance of considering specific characteristics of the potential treatment target lobe when selection patients for endobronchial valve treatment.

Revision bronchoscopies, granulation tissue, and release of nickel

In **chapter 7** we assessed the need for revision bronchoscopies after endobronchial valve treatment. In a cohort of 179 patients, we established that 41% of patients required at least one revision bronchoscopy, mainly due to the loss of the initial treatment effect. The predominant finding during these bronchoscopies was the formation of granulation tissue. While endobronchial valves were replaced in most cases, permanent removal of all valves was necessary in 13% of cases. Our results highlight that there is a considerable demand for revision bronchoscopies post-treatment, predominantly due to the formation of granulation tissue. This underscores the importance of enhancing our understanding of this phenomenon and the potential risk factors associated with it.

In **chapter 8** we aimed to identify potential risk factors associated with the formation of granulation tissue following the implantation of airway devices, including endobronchial valves and airway stents, through a comprehensive literature review. Despite limited research on this topic, suggested risk factors included procedural-related tissue injury, the presence of micro-organisms, device-related factors such as material, design, and sizing to the airway diameter, and patient-related factors such as genetic susceptibility, comorbidities, and medication use. However, our review primarily emphasized the scarcity of research into this topic, underscoring the need for further investigation to enhance our understanding and to identify potential risk factors associated with granulation tissue formation.

In **chapter 9** we evaluated whether inappropriate endobronchial valve sizing, either oversizing or undersizing, is a risk factor for granulation tissue formation. We compared the size of 449 individual endobronchial valves, implanted in 188 patients, to the corresponding CT-derived airway lumen diameter. We observed that 52% of the implanted valves were oversized compared to the diameter of the airway lumen, quantified on the pre-treatment CT scan. However, there was no significant difference in the number or proportion of oversized valves in patients with and without diagnosed granulation tissue. Consequently, we could not confirm the hypothesis that inappropriate valve sizing is a risk factor for granulation tissue formation.

In **chapter 10** we studied the release of nickel from implanted endobronchial valves into adjacent lung tissue. Our study used surgically removed lung tissue samples from a patient previously treated with endobronchial valves and we compared these with samples for a control patient who had never undergone treatment with any lung implantable device. Additionally, we considered nickel concentrations in lung tissue reported in the existing literature. Our analysis showed no significant difference in nickel concentration between the treated and the control patients, and the observed concentrations aligned with the reported levels in the literature. This suggests that endobronchial valves may not release substantial amounts of nickel in the lungs. Consequently, patients with a known nickel hypersensitivity might safely undergo treatment without triggering averse nickel-related effects.

Lung volume reduction coil treatment

Chapter 11 provides a systematic review and meta-analysis of trials assessing the efficacy of bronchoscopic lung volume reduction coil treatment using the RePneu lung volume reduction (LVR-) coil. Eight trials, including four randomized controlled trials and four single-arm trials, were identified, and shared individual participant data. Our meta-analysis indicated that treatment with these LVR-coils resulted in sustained improvements in pulmonary function and quality of life, along with shorter-lived improvements in exercise capacity. However, treatment was associated with an increased risk of respiratory adverse events, particularly exacerbations of COPD, without a higher risk of death. Unfortunately, the production of the RePneu LVR-coil has stopped and therefore this treatment is currently unavailable. However, this discontinuation drove the development of newer generations of coils.

In **chapter 12** we explore one of the potential successors of the RePneu LVR-coil, the Lung Tensioning Device (LTD-) coil #4. We performed a prospective single-arm study involving 14 patients to evaluate the feasibility, safety, and efficacy of LVR-coil treatment in patients with advanced emphysema and substantial hyperinflation. Our findings indicate that LTD-coil treatment is feasible and showed a safety profile comparable to the previous LVR-coil. Although the treatment led to a significant reduction in the inspiratory and expiratory volume of the treated lobes on the CT scan and improvements in quality of life, it did not result in significant enhancements of pulmonary function or exercise capacity. This outcome raises the question of whether the LTD-coil can be considered as a potential successor to the previous LVR-coil.