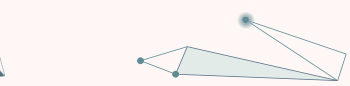
CHAPTER

14

General discussion and future perspectives



GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition requiring a personalised treatment approach which should involve the identification of treatable traits based on the predominant symptoms and the patient's specific endotype and phenotype [8, 202]. For COPD patients characterized by advanced emphysema, hyperinflation can be one of those treatable traits. If these hyperinflated COPD patients continue to experience significant dyspnoea despite optimal pharmacological and nonpharmacological therapies, bronchoscopic lung volume reduction can be a valuable additional treatment option. The aim of this thesis was to enhance the understanding of and refine bronchoscopic lung volume reduction treatments, with a particular emphasis on endobronchial valve and lung volume reduction coil treatments.

One-way endobronchial valves

Predictors of response

Succes of bronchoscopic lung volume reduction using one-way endobronchial valves is closely tied to patient and target lobe selection. Eligible patients have advanced emphysema, are limited by hyperinflation, have a suitable target lobe without collateral ventilation, and are not affected by comorbidities associated with possible negative treatment outcomes [22]. Considering the substantial costs, potential complications, the impact of treatment failure on a patient, and the limited alternative treatment options, it becomes evident that careful patient selection is crucial.

Despite advancements in experience and tools, such as quantitative computed tomography (CT) scan analysis, a subset of patients fails to experience meaningful improvements. Our findings suggest that within our current routine care population, characteristics of the target lobe play an essential role as primary predictors of treatment response (chapter 6). The target lobe of responders exhibits more emphysematous destruction and air trapping, less perfusion, and greater heterogeneity in destruction and perfusion compared to the ipsilateral nontargeted lobe. Notably, when evaluating destruction heterogeneity in isolation, it serves as a predictor of response magnitude rather than treatment response in general (chapter 5). This underscores the necessity of evaluating all patient and target lobe characteristics combined rather than in isolation. However, the specific parameters that carry more weight in predicting treatment response remain currently unknown. It could be hypothesized that in patients with a more homogeneous distribution of emphysema the characteristics of the nontargeted lobes are more important for overall treatment response than in patients with a more heterogeneous distribution, considering that for the same target lobe destruction, the overall quality of the remaining lung tissue is worse in patients with a homogeneous distribution. Consequently, perfusion and air trapping of the target lobe compared to all other lobes might be more important predictors of response in the case of more homogeneous emphysema.

To optimize future patient selection, artificial intelligence (AI) emerges as a promising tool. AI-based algorithms are already used in quantitative CT scan analysis, and numerous advances have been seen over the years. These developments have expanded the parameters quantifiable on the CT scan, now including perfusion and pulmonary function measures [119, 203]. The widely used StratX® report currently reports fissure completeness, voxel density (emphysematous destruction) at -910 and -950 Hounsfield Units, and inspiratory volume. Integrating the additional parameters derived from the CT scan that were significantly different between responders and nonresponders, could assist in and enhance patient and target lobe selection. We propose a newer version of the StratX® report, which is illustrated in figure 1. Furthermore, the rapid progress in AI technology also holds potential for the development of algorithms capable of predicting endobronchial valve treatment response using the pre-treatment CT scan and pulmonary function test outcomes. Such algorithms could consider and weigh all parameters associated with treatment response, providing particularly beneficial for borderline-eligible patients.

	Right lung				Left lung	
	RUL	RUL+RML	RML	RLL	LUL	LLL
% Fissure completeness	100	100	100	100	100	100
% Voxel density less than -950 HU	47	43	36	47	28	39
Inspiratory volume (mL)	1248	1986	738	1519	1571	1639
Expiratory volume (mL)	991	1554	563	1180	1010	1271
Expiratory/Inspiratory volume ratio (%)	79	78	76	78	64	78
% Perfusion	12	12	12	22	30	24
% Air trapping less than -856 HU	77	76	75	73	55	69
Lung volumes	TLC 6.7 L (123% pred)		RV 5.0 L (256% pred)		RV/TLC 75%	

Figure 1. Proposal for newer version of the StratX® report. This proposed version introduces new variables, including expiratory volume, expiratory/inspiratory volume ratio, perfusion, air trapping, and CT-derived lung volumes (TLC, RV, and RV/TLC ratio). In the current StratX® report, the only distinguishing factor between the RUL and RLL is the inspiratory volume. The addition of the new variables reveals a lower perfusion and more air trapping of the RUL compared to the RLL. This suggests that the RUL may be a more suitable target lobe for endobronchial valve treatment based on the quantitative CT analysis alone. RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe, HU = Hounsfield Units, mL = milliliter, TLC = total lung capacity, RV = residual volume, L = liter, % pred = percentage of predicted.

Long-term treatment outcomes

Multiple randomized studies have consistently confirmed the effectiveness of endobronchial valve treatment, demonstrating sustained benefits for up to one year post-treatment [28, 32, 141, 204]. Recent research has indicated that improvements can persist for at least three years, despite the progressive nature of COPD [32, 205, 206]. To prolong treatment effect, revision bronchoscopies are crucial in a large number of patients as we have shown that around 40% of patients require at least one within 18 months after endobronchial valve treatment and in more than half of these patients granulation tissue formation was observed and frequently caused loss of the initial treatment effect (chapter 7). This emphasized the need to understand the biological mechanism and the risk factors associated with granulation tissue formation after endobronchial valve implantation.

Based on the limited available literature, we have proposed a model with hypothetical risk factors for the formation of granulation tissue which included patient-, device, procedure-, and microorganism-related factors (chapter 8). From this model we have explored two potential causes: airway colonization pre- and post-treatment (chapter 7) and in appropriate valve sizing to the airway lumen, i.e. over- or undersizing (chapter 9). However, no association between these factors and granulation tissue formation was identified. An ongoing prospective clinical trial (Bio-EXCEL, NCT04214587) aims to enhance the understanding through tissue and blood sample collection from patients requiring a revision bronchoscopy and those with sustained treatment benefits. This trial holds the potential to deepen our insights into granulation tissue formation post-device implantation and drive advancements to improve the device, the implantation procedure or patient management, with the goal of limiting granulation tissue formation.

A probable risk factor for the formation of granulation tissue post-endobronchial valve implantation could be the outer silicone layer of the valve. Silicone is widely used in medical products and implants due to its desirable properties, including flexibility, low toxicity, cost-effectiveness, and biocompatibility [207]. However, the biocompatibility of silicone is compromised as silicone is susceptible to the adherence of proteins, which can subsequently modulate an immune response, stimulating the formation of granulation tissue. A recent study has shown, in explanted endobronchial valves. that a numerous proteins adhere to the silicone surface [188]. Therefore, a potential solution to minimize granulation tissue formation after treatment with endobronchial valves might involve changing this silicone layer. This might be achieved by using a different material that is less susceptible to protein adherence or, inspired by the advances in coronary stents [208], a drug-eluting endobronchial valve that either limits protein adherence and/or minimizes the immune response that causes the formation of granulation tissue. Future research is needed to determine if this is a potential option and what materials or drugs would be of interest.

Alternative bronchoscopic lung volume reduction options

Unfortunately, many patients are ineligible for endobronchial valve treatment, mainly due to the presence of collateral ventilation, emphasizing the need for alternative bronchoscopic lung volume reduction options independent of fissure integrity or techniques to close fissure defects [109, 209].

Lung volume reduction coils

Lung volume reduction coils are a collateral ventilation-independent bronchoscopic technique which has been the most extensively researched, next to endobronchial valves. The first developed coil, the RePneu coil (PneumRx/BTG), demonstrated sustained improvements in residual volume reduction and quality of life up to 12-months post-treatment but shorter-lived improvements in reduction of airflow obstruction and exercise capacity (chapter 11). However, there was a large variability in treatment response and although some predictors of response have been identified, treatment response was harder to predict than with endobronchial valves [36, 40, 158, 192]. Furthermore, coil treatment increases the risk of respiratory adverse events, mainly acute exacerbations of COPD and pneumonia, and the treatment is irreversible. These outcomes combined with the discontinuation of the RePneu coil drove the development of newer generation coils.

The lung tensioning device (LTD) coil #4 (FreeFlow Medical, USA) has a different three dimensional orientation than the previous coil, but, despite a similar safety profile, did not significantly improve pulmonary function or exercise capacity (chapter 12). In line, the Cinenses lung volume reduction reverser (LVR-R, Lifetech Scientific, China), also with a different three-dimensional orientation and coverage by a polymer, similarly did not significantly enhance efficacy outcomes [210, 211]. Based on the previously reported positive effects of the RePneu coil design, currently, a coil almost identical to the previous RePneu coil, the LTD-coil #2 (FreeFlow medical, USA), is available and apparently is being used outside clinical trials in Germany and Switserland. Whether the newer coil designs will ever make it outside the context of clinical trials remains uncertain, especially if the coil with the previous design becomes more widely available or if newer, possible more effective, bronchoscopic lung volume reduction treatments are developed, such as the newer 'stent-like' devices that are currently under investigation.

Other bronchoscopic lung volume reduction options

Airway bypass stents were designed to create permanent transbronchial passages in areas with significant air trapping. Despite initial significant improvements post-treatment, the inability to maintain stent patency led to short-lived benefits [20]. Currently, newer 'stent-like' devices, such as the Apreo implant (BREATHE-2: NCT05949645) and the Implantable Artificial Bronchus (IAB-1: NCT05087641), are under clinical investigation. These devices are designed to keep the airways open, allowing trapped air to escape and subsequently reduce hyperinflation. Importantly, these devices do not require the absence of collateral ventilation and could be removed in the initial post-implantation period, which are desired properties

for a bronchoscopic lung volume reduction device. However, potential challenges with these devices might include obstruction of the device-lumen by mucus or granulation tissue, which could lead to infections or loss of effect. The Apreo implant is composed of nitinol, a material well-known for lung-implants as it is used for both endobronchial valves and coils. On the other hand, the IAB is composed of polyether-ether-ketone (PEEK), a material not previously used in lung-implantable devices. Although PEEK is suggested to be a successor for metals used in medical devices and has been used in dental and orthopaedic implants [212], its effect on lung tissue remains unknown and might be a factor that limits the effectiveness of the IAB. Ongoing and future trials will determine the safety (long-term) efficacy, and the challenges associated with these novel devices.

Another bronchoscopic lung volume reduction method that has been investigated involves inducing a local inflammatory response using either heated water (thermal vapour ablation) or lung adhesives (sealants) which subsequently leads to fibrosis and subsequent lung volume reduction of the treated areas [213, 214]. While both methods resulted in significant improvements, a relatively high rate of serious respiratory adverse events combined with the permanent nature of these treatments has hindered further large investigations and clinical applicability. Potential improvements reducing the adverse effects might be achieved if the instigated inflammatory response is less pronounced. However, it remains questionable whether a milder response will also result in the desired treatment outcomes.

Lung adhesives (sealants) are currently also under investigation to close small fissure defects (Mind The Gap: NCT04256408, CONVERT: NCT04559464, and CONVERT II: NCT06035120). This approach aims to reverse collateral ventilation status, potentially allowing subsequent treatment with endobronchial valves. The effectiveness of this concept has been confirmed for the left fissure in a small study [215]. However, the lung adhesives still involves a toxic crosslink compound to initiate an inflammatory response and induces fibrosis formation for closing the fissure defects. However, the formation of fibrotic tissue is not instantaneous, necessitating repeat bronchoscopies: at least one to apply the lung adhesives and close the fissure gap, and another to implant the endobronchial valves. To optimize this approach, there is a critical need for a less toxic and nearly instantaneous working adhesive capable of closing fissure defects and allowing for endobronchial valve implantation during the same bronchoscopic procedure. This would not only reduce the number of bronchoscopies but also potentially decrease the risk of adverse events in this fragile patient population.

MAIN CONCLUSIONS

Over the past decades, bronchoscopic lung volume reduction has proven to be a valuable additional treatment option for advanced emphysema, with one-way endobronchial valves leading the way as the only option that has advanced beyond the clinical trial stage. Further refinement of this treatment requires a deeper understanding of the significance of the various characteristics, especially those related to the target lobe, in treatment response. Additionally, to extend the longevity of the treatment effect and possibly reduce the need for revision bronchoscopies, in-depth insights into granulation tissue development is required. Unravelling this complex phenomenon, the underlying biological mechanisms, and associated risk factors might be the key to driving improvements in the design of endobronchial valves, the implantation procedure or patient management. For patients ineligible for endobronchial valve treatment, alternatives are still warranted. Lung volume reduction coils might be a possibility, but there is a lack of advances in recent years, combined with the unpredictable treatment response and permanent nature also opens the possibility for alternative devices such as the devices designed to keep the airways open (APREO, IAB). However, ongoing and possible future trials need to provide insights into the safety, efficacy, and challenges associated with treatment with these novel devices.