Bronchoscopic lung volume reduction

Klooster, Henderika

CHAPTER

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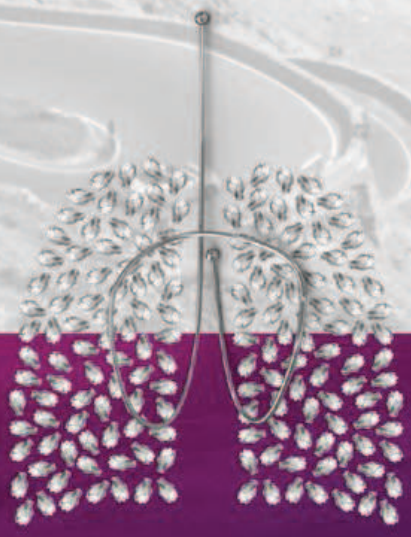


Discussion and future perspectives

Discussion

The key message of this thesis is that bronchoscopic treatment with endobronchial valves in selected patients with emphysema significantly improves pulmonary function, exercise capacity, and quality of life. The endobronchial valve treatment can be considered as an additional treatment option next to optimal conventional medical treatment for patients with COPD and with very severe emphysema preselected to have proven absence of interlobar collateral ventilation. For patients who are not qualified for endobronchial valve treatment the coil-treatment has been shown to be a valid treatment option. However, its real efficacy and safety profile needs to be further evaluated in randomized controlled trials with larger sample sizes and longer follow-up.

For patients with very severe COPD, who are on optimal medical treatment, additional surgical treatments can be considered. Lung transplantation is one, but its availability is very limited due to the scarcity of donor lungs, and also patients are not allowed to have major co-morbidities or other surgical restrictions. Lung volume reduction surgery is also an effective treatment, but only in a very small group of carefully selected patients. Further investigation is necessary to establish how bronchoscopic intervention should be positioned relative to lung volume reduction surgery and lung transplantation. We postulate that bronchoscopic lung volume reduction can act as a bridge to one of the surgical interventions in some, and as an alternative cheaper, and more accessible option in other patients with advanced emphysema.

Endobronchial valve treatment

In the STELVIO trial we demonstrated that endobronchial valve treatment significantly improved lung function, exercise capacity, and quality of life compared to usual care. In this prospective randomized controlled trial the earlier published open label and post-hoc best responder profile of endobronchial valve treatment was confirmed. In our trial, patients were pre-selected on having complete- or near complete fissures on HRCT scan, after which an additional 15% of the patients for endobronchial valve treatment were excluded by Chartis assessment because of collateral ventilation. We previously reported that these collateral ventilation-positive patients would not benefit from the endobronchial valve treatment.[1] A recently published study, the BeLieVeR HIFi study[2], also showed that patients with intact interlobar fissures on CT scan but with presence of collateral ventilation measured with the Chartis system did not experience benefit from endobronchial valve treatment. Therefore, endobronchial valve treatment in selected patients with very severe emphysema and with proven absence of interlobar collateral ventilation should be considered as an additional treatment option besides the conventional treatment. This accurate selection of patients is in our opinion a perfect example of personalized or precision medicine.

Effective therapies are never without side effects. Pneumothorax was the most frequently occurring adverse event. The occurrence is commonly thought to be due to the rapid shift in lung volumes causing rupture of a bleb/bullae either due to barotrauma, or due to pleural adhesions. Because a pneumothorax potentially is a life threatening complication

in severe emphysema, close monitoring of patients after endobronchial valve treatment is crucial. In the STELVIO trial the median hospital stay after treatment was one day. In our clinical practice today we have expanded the inpatient hospital stay to at least five nights after endobronchial valve treatment to monitor for the occurrence of life threatening pneumothorax. Furthermore, pneumothorax may also occur in a later phase.[3,4] and therefore patients need to be provided with clear instructions also after discharge.

Repeated bronchoscopy is sometimes necessary to either replace temporarily or remove permanently the endobronchial valves. Reasons to do so include loss of initial lung volume reduction due to formation of granulation tissue leading to leakage or valve migration. Previous studies postulated that endobronchial valve treatment is fully reversible and does not preclude future therapeutic options. Our study confirms this opinion, since all patients in whom endobronchial valves were removed recovered without further side effects.[5,6,7]

The data of our study showed that the endobronchial valve treatment is effective up to 6 months. Two small uncontrolled case-series have now shown sustained improvements up to two years after endobronchial valve treatment.[8,9] Where for lung volume reduction surgery long term survival benefit and improved exercise capacity has been demonstrated in selected patients[10], for endobronchial valve treatment, long-term effectiveness still needs to be proven.

Lung volume reduction coil treatment

The second aim of the thesis was to investigate the feasibility and efficacy of a new experimental treatment, the placement of coils in patients with severe emphysema. In 3 sequential studies we showed that this coil treatment is a promising technique both in patients with heterogeneous- as well as homogeneous emphysema. The treatment is technically feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life with sustained results at 1 year. However, in our very first ever treated patients with coils, the clinical benefit gradually declined over a 3 year period. The coil treatment has an acceptable safety profile without long-term unexpected device related adverse events.

Serious adverse events mainly occurred in the first 30 days after the procedure. The total rate of these events following endoscopic implants did not exceed the number of exacerbations and pneumonias that were reported in the sham-control bronchoscopy group of the EASE trial.[11] Lung volume reduction coil procedure related events that occur are typically very mild hemoptysis or mild chest discomfort, both for a few days and requiring no intervention. In our studies reported here, we encountered no deaths or coil related consolidations, but these did occur in other studies.

In our study, broad selection criteria were purposely used in order to evaluate the effectiveness in a population of patients representative of the patients we see in daily practice. We hypothesized that this may be one of the reasons for the large variability of response between patients. However, a significant responder rate of approximately 50-60%

was found for several clinical endpoints. To better understand the predictors of response to lung volume reduction coil treatment, we conducted a multivariate analysis to assess the relationship between the response to treatment and baseline variables typically identified as predictors of outcome, such as hyperinflation and emphysema heterogeneity. Using the 6 month endpoints, none of the evaluated baseline variables provided a meaningful predictor of response to lung volume reduction coil treatment. Other potential variables could include more nuanced emphysema phenotypes beyond heterogeneous or homogeneous classification, such as the presence of small airways disease, and variability in coil placement strategies such as exact position, length and number of coils used. A recently published meta-analysis using all raw lung volume reduction coil trial data in a larger patient cohort (N=140) identified higher residual volume at baseline as the only independent predictor of treatment succes.[12]

When comparing the results for patients with upper lobe versus lower lobe lung volume reduction coil treatment, a trend in the outcome differences was observed in favor for upper lobe treatments.[12] However, to date only a small number of patients has been treated in the lower-lobes, and the lower FEV_1 results seen with lower lobe coil treatments is comparable to the experience with lung volume reduction surgery in the lower lobes where the effect on improving FEV_1 is also limited compared with other outcome variables.[13] However, in general the FEV_1 shows a weak association with exercise performance in patients with severe emphysema.[14] Future research is needed to evaluate whether, as currently hypothesized, the much bigger lower lobes require a greater number of coils to optimize results.

Lung volume reduction coil treatment proved efficacious both in patients with heterogeneous and with homogeneous. The primary mechanism of action of coils appears to be mechanical re-tensioning of the lung matrix, rather than just reducing absolute lung volume alone. In the studies reported in this thesis, we observed a significant decrease in airway resistance after lung volume reduction coil treatment. Beforehand, one might expect that implantation of coils inside the airways would obstruct airflow and increase airway resistance. Apparently, the mechanical properties of the lung are improved by the treatment and, importantly, our study also suggests that the lung parenchyma in subjects with homogeneous emphysema is still healthy enough to transfer the elastic recoil forces to the airways. Despite this interesting observation, additional studies are necessary to better characterize the mechanisms of action of the coil treatment, and thereby to better identify responders to coil treatment. Furthermore, future research needs to confirm the efficacy of the coil treatment in homogeneous emphysema, which represents a large number of patients usually excluded from other surgical and bronchoscopic lung volume reduction treatment options.

The lung volume reduction coil trials presented in this thesis were uncontrolled studies and therefore susceptible to potential bias. However, we have previously shown that even in a sham controlled bronchoscopic interventional trial design, only a small placebo effect was observed in patients with severe COPD.[11] Nevertheless, one of the next steps should be to confirm the results in a prospective, multicenter, randomized, controlled study to compare efficacy outcomes between the coil treatment and standard of care. The results

of a French N=100 patient's multicenter 1:1 randomized study comparing coils with usual care were recently published. At 6 months, lung volume reduction coil treatment was associated with a significant decrease in hyperinflation and sustained improvement in quality of life.[15] Another study (called RENEW) is being conducted since December 2012. The first brief preliminary results of this N=315 patient's multicenter randomized controlled trial were made public in December 2015 by the study sponsor PneumRx/BTG. All primary and secondary endpoints of the study were met. Analysis showed statistically significantly greater improvements in the treatment group than in the control group from baseline to 12 months: the increase in the distance on 6 minute walk test was greater by 10.2 meter (P=0.015), the increase in FEV_1 was greater by 8.8% (P < 0.0001). Improvements were also seen in SGRQ scores with a -8.9 points greater reduction in the treatment group than in the control group (P<0.0001). Serious adverse events associated with bronchoscopy and coil placement such as pneumothorax, lower respiratory tract infections, respiratory failure, hemoptysis, COPD exacerbation, and dyspnea occurred at a higher rate in the treatment arm, as anticipated.

Role of dynamic hyperinflation

The final aim of this thesis was to determine the role of dynamic hyperinflation in patients with severe COPD. We assessed whether the manually paced tachypnea test, sitting at rest, is feasible also in patients with severe COPD, and whether the induced dynamic hyperinflation correlates with exercise performance in these patients. We indeed demonstrated good feasibility for the use of the manually paced tachypnea test to induce dynamic hyperinflation in a group of patients with severe COPD. Static hyperinflation in this severe group seemed to be to be a better predictor of exercise performance than dynamic hyperinflation. We believe that the observed negative association between dynamic hyperinflation and exercise capacity is attributable to the more severe disease state of our patient population. All the patients in our study were referred and evaluated for bronchoscopic lung volume reduction treatment and were diagnosed with severe static hyperinflation. Additionally, it would be interesting to also investigate dynamic hyperinflation after a bronchoscopic treatment; our studies demonstrated that static hyperinflation decreases after successful bronchoscopic lung volume reduction treatment.

Patient selection for bronchoscopic lung volume reduction treatment

We have shown that bronchoscopic lung volume reduction can be an additional treatment option for patients with advanced emphysema. Nevertheless, pharmacological treatment, pulmonary rehabilitation, as well as smoking cessation remain the basis of treatment for COPD. When a patient with advanced emphysema still experiences severe complaints despite optimal medical management, a bronchoscopic lung volume reduction treatment can be considered. From previous trials we have learned that patient selection is paramount for correctly identifying candidates who will benefit from a bronchoscopic lung volume reduction treatment. In other words: not every patient with severe COPD is suitable. For example, a patient with a predominant chronic bronchitis phenotype of COPD is not suitable for lung volume reduction treatment.

Therefore, a stepwise approach is needed to evaluate the most suitable treatment option for the individual patient.

Our approach is to carefully evaluate each individual patient, and use at least information about:

- Burden of the disease and motivation to contribute to improvement
- Presence of co-morbidity
- Severity of airway obstruction and hyperinflation
- Radiological assessment of emphysema and fissure integrity

Burden of the disease and motivation to contribute to improvement

A patient with advanced emphysema should have severe complaints despite optimal medical management, and experience poor quality of life and reduced exercise performance, to be selected for bronchoscopic treatment. Also patients who are highly motivated to improve their health status and are trying to keep as physically active as possible, and follow a supervised exercise program before the intervention are potential candidates.

Presence of co-morbidity

Patients with co-morbidities, such as severe pulmonary hypertension, significant heart failure, or severe chronic respiratory failure are not eligible for a bronchoscopic lung volume reduction treatment. The bronchoscopic interventions are performed under either deep conscious sedation or general anesthesia, and the treatments do not come without adverse events. Patients will have to be fit enough to sustain the procedure and to survive adverse events. Also significant co-morbidity can contribute notably to the patient's symptoms in such a way that a bronchoscopic treatment does not relieve these. Furthermore, patients with repeated infections of the lower airways and frequent exacerbations of COPD, are not eligible for treatment. Foreign, blocking material can induce even more infections. It is important to note that a bronchoscopic lung volume reduction treatment is only suitable for patients in a stable disease phase, thus it cannot be advised to be used as an emergency treatment.

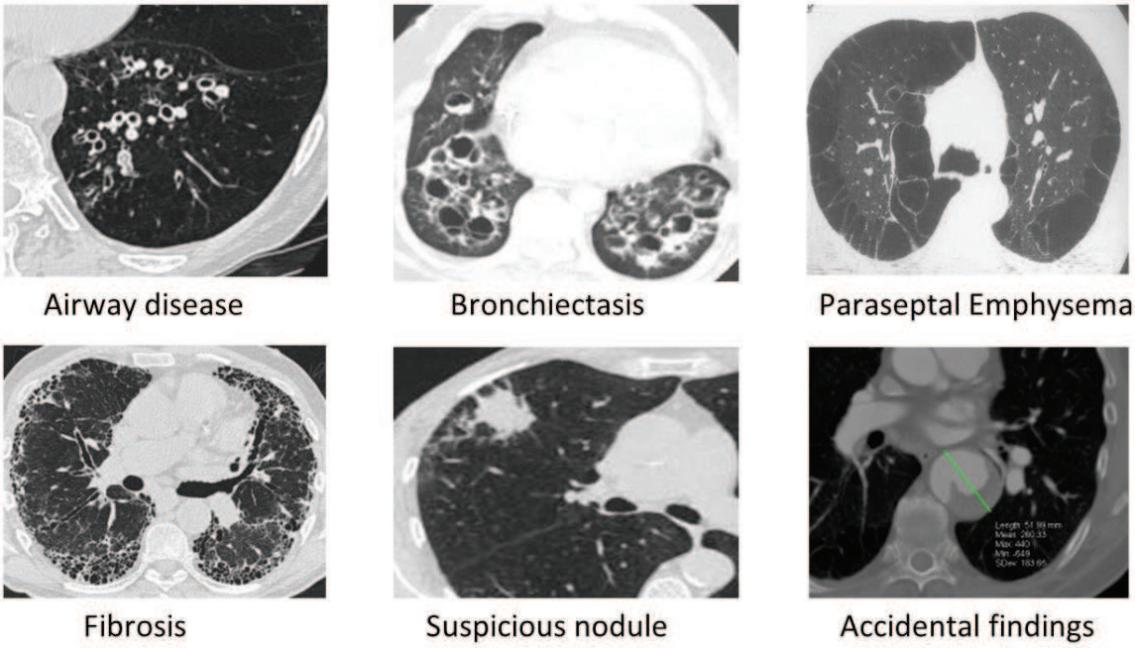
Severity of airway obstruction and hyperinflation

There is no full consensus on criteria for lung function. To be eligible for many of the bronchoscopic lung volume reduction studies performed so far, patients needed an FEV_1 between 15% and 45% of predicted, which is also what we adhere to. Additionally patients should have significant hyperinflation as measured by bodyplethysmography. The residual volume should be above 175% of predicted and the total lung capacity above 100% of predicted. Preferably also the residual volume/total lung capacity ratio should be above 55%.

Radiological appearance of emphysema

A thin slice (≤1mm) volume CT scan (without contrast) is absolutely required in the selection procedure for bronchoscopic lung volume reduction. First a primary assessment should be performed to ensure the absence of abnormalities such as significant airway disease

(bronchial wall thickening, bronchopathy, bronchiectasis), paraseptal emphysema, lung fibrosis, or a suspicious nodule. When these findings appear, the patient is not eligible for a lung volume reduction treatment even when the pulmonary function shows eligibility. The figure below presents examples of abnormalities in the lung disqualifying the patient for bronchoscopic lung volume reduction treatment.



In case there are no significant abnormalities deteced on the HRCT an assessment should be performed to characterize the emphysema and to evaluate the distribution (homogeneous or heterogeneous) and the percentage of parenchymal destruction expressed as the proportion of pixels. Patients with a parenchymal destruction less than 50% in the potential treatment target are not suitable for endobronchial valve treatment or lungvolume reduction surgery. Patients with a parenchymal destruction more than 75% are not suitable for coil treatment (See figure “Overview of a quantitative emphysema score” in the introduction section of this thesis).

Finally, fissure integrity should be assessed, since this will guide the appropriate treatment option. The exact radiological completeness of the lobar fissure necessary for an effective treatment is not well known. The current data indicates that valve treatment is not effective if the interlobar fissure between the treatment target lobe and adjacent lobe is less than 85-90%, because of the high probability of presence of collateral ventilation. Patients with an incomplete fissure should not be considered for treatment with endobronchial valves but may be eligble for lung volume reduction coil treatment.[16]

If the interlobar fissure between the treatment target lobe and adjacent lobe is more than 85% intact, the absence of collateral ventilation can be confirmed by measurement of collateral ventilation with the Chartis system. When using this combined approach of assessment of fissure integrity on CT and the Chartis measurement, a responder rate of approximately 75% can be achieved.[17]

Summary of patient selection for bronchoscopic lung volume reduction treatments

A summary of the current main inclusion and exclusion for lung volume reduction treatments in our hospital is presented in the following figure. Patients who fulfill these inclusion and exclusion criteria could be presented to a multidisciplinary team including a radiologist, pulmonologist and interventional pulmonologist. In this team the pro and cons of the various treatment options should be discussed, like a wait and see approach, endoscopic lung volume reduction, lung volume reduction surgery and lung transplantation. Importantly, future lung transplantation is not a contraindication for bronchoscopic lung volume reduction.[18]

INCLUSION

Diagnosed with COPD
- Emphysema phenotype
- Symptomatic (mMRC>1)

Medical treatment
- Optimal pharmacological treatment
- Post-rehabilitation and/or maintenance (supervised) physical activity
- Stopped smoking for at least 6 months
- Vaccination
- Optimal nutrition

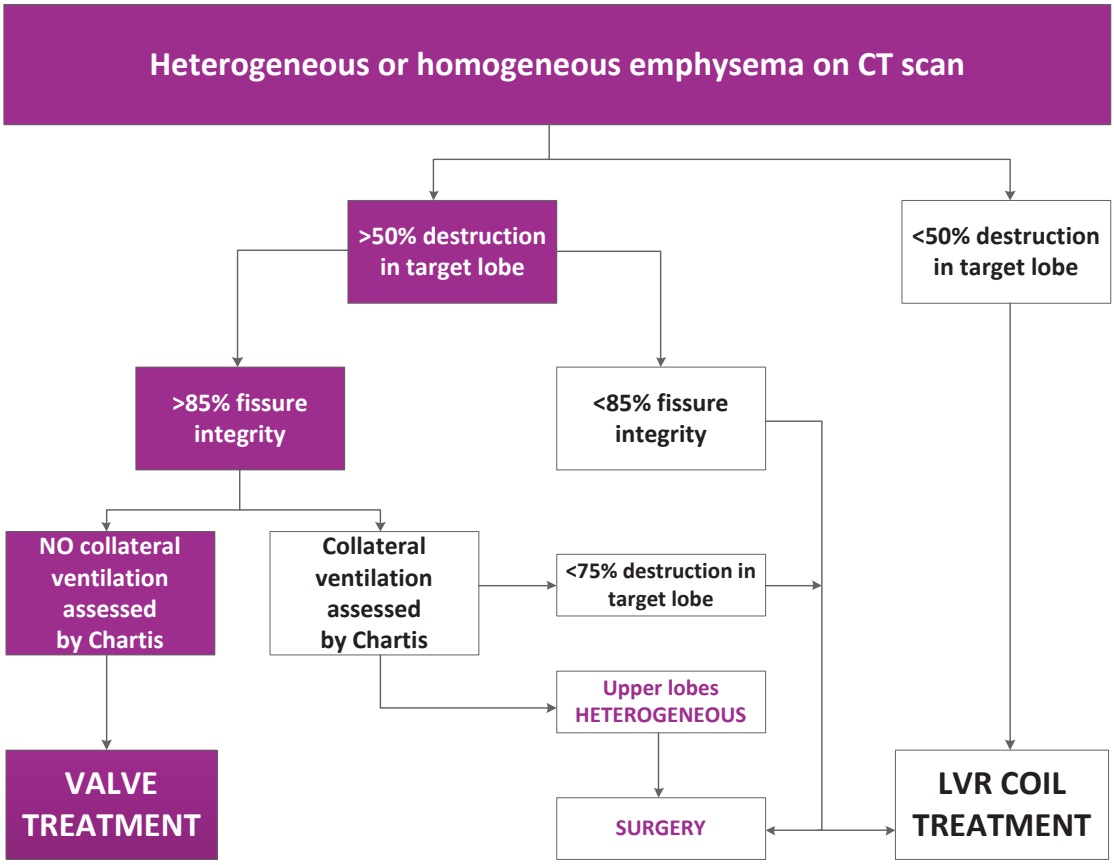
Pulmonary function testing
- FEV_1 % predicted between 15% and 45%
- Residual volume % predicted >175%
- Total lung capacity % predicted >100%
- Residual volume/total lung capacity >55%

EXCLUSION

- Chronic bronchitis phenotype
- Clinically significant bronchiectasis
- Frequent exacerbations
- Previous lobectomy, pneumonectomy, lung volume reduction surgery or lung transplantation
- Significant abnormalities on CT scan, such as severe paraseptal emphysema, fibrosis and suspicious nodule
- Severe hypercapnia ($PaCO_2$>8kPa)
- Severe hypoxia (PaO_2 <6.0kPa)
- Pulmonary hypertension (right ventricle systolic pressure >50 mmHg)
- Heart failure (left ventricle ejection fraction <40%)
- Maintenance anticoagulation: coumarines, low molecular weight heparin, clopidrogel or similar antiplatet agents, direct thrombin inhibitors

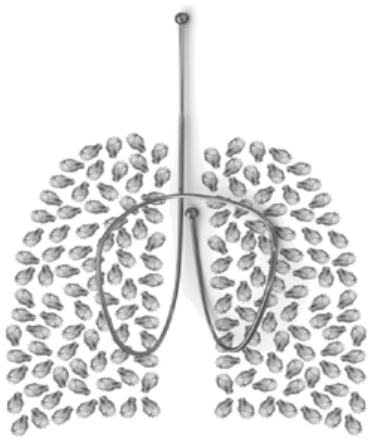
'The Groningen' treatment algorithm

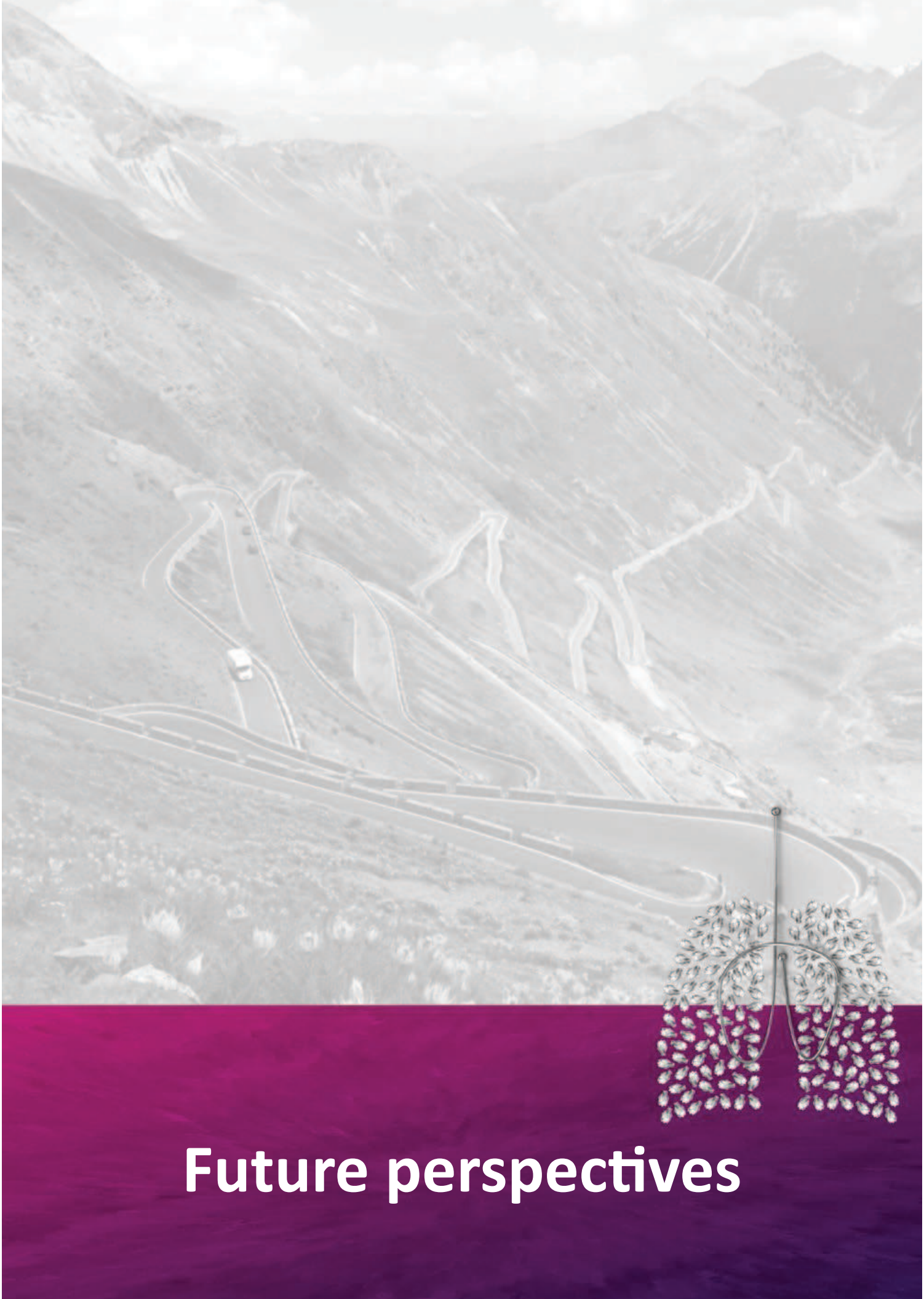
The treatment algorithm shown in the following figure shows the different treatment options for patients fulfilling the described inclusion and exclusion criteria.



Choice of treatment depends on the severity of parenchymal destruction, fissure integrity (both performed by visually assessment) and presence or absence of collateral ventilation confirmed with the Chartis system. Nevertheless, when taking these steps together, the final treatment recommendation is personalized medicine in these patients with severe emphysema. Other factors such as the severity of hyperinflation and the degree of heterogeneity can further influence the choice of treatment. The algorithm is a guidance to treatment which is based on the available literature and experiences from our hospital.

Currently, only lung volume reduction surgery and endobronchial valve treatment have reached the evidence level to be used outside clinical trials. For these techniques, as well as for the not fully proven newer techniques, keeping good registries in limited centers employing the technique is probably wise in order to ensure enough number of interventions with excellent expertise, to expand the evidence base, and to support and guide the reimbursement process of these therapies.





Future perspectives

Future perspectives

In this thesis new treatment modalities for patients with severe emphysema were investigated, however, there are still many challenges for future research.

Pneumothorax associated with endobronchial valve treatment

The important benefit of bronchoscopic lung volume reduction using endobronchial valves, comes with a significant risk of a pneumothorax. In approximately one out of four patients treated with endobronchial valves a pneumothorax occurred. In patients with severe emphysema a pneumothorax potentially is a life threatening complication and needs close monitoring of patients after endobronchial valve treatment. The occurrence is commonly thought to be due to the rapid shift in lung volumes causing rupture of a bleb/bullae either due to barotrauma, or due to pleural adhesions.[4]

The presence of pleural adhesions in the target lobe on CT scan might provide prognostic information about likelihood of future pneumothorax occurrence, and this can be assessed on existing scans of patients prior to having had a procedure. Furthermore, strenuous activity or coughing might also lead to higher risk of pneumothoraces.[19] To decrease the pneumothorax incidence it might be useful to modify post-treatment medical care to include bed rest for 48 hours and provide cough suppression after bronchoscopic lung volume reduction with valves. However, probably this will not prevent pneumothoraces in a later phase.[20] Future research will certainly increase our knowledge on pneumothorax occurrence. A prospective, randomized study will be needed to confirm if modified post-treatment medical care, perhaps especially in higher risk patients as determined by pre-procedural CT scans, can actually reduce pneumothorax occurrence.

Blocking collateral ventilation

The majority of patients with heterogeneous emphysema has collateral ventilation and is therefore not suitable for endobronchial valve treatment. If we could close the collateral channels and afterwards perform an endobronchial valve treatment, the overall efficacy of bronchoscopic lung volume reduction would improve and a larger group of emphysema patients could be served. Autologous blood can be a potential substance to close off these collateral channels. The proposed mechanism is that the instilled autologous blood induces a mild inflammatory reaction, which combined with clotting itself, leads to scarring, fibrosis and the closing of the collateral channels. The use of autologous blood in the treatment of giant bullae in patients with emphysema has shown promising results, though admittedly the underlying pathology was different. Nevertheless, the treatment was safe and minimally invasive.[21] Furthermore, autologous blood is used in the treatment of a persistent air leak for example primary pneumothorax [22] and in some countries where there is no access to devices, lung volume reduction is conducted with autologous blood.[23] The advantage of the use of patient's own blood is that there are almost no device or experimental substance costs. A prospective, safety and feasibility study is needed to investigate if autologous blood, or another obLiterating agent, can be used to close the collateral channels.

Treatment for COPD patients with the bronchitis phenotype

Patients with the emphysema phenotype have parenchymal destruction and are therefore potential candidates for bronchoscopic lung volume reduction. Patients with the bronchitis phenotype, whether or not also with marked emphysema, have significant sputum production and sometimes frequent exacerbations with often better preserved lung tissue. Those patients are not eligible for endobronchial valve or coil treatment, due to the increase of infectious complications. We recently performed the first-in-human study investigating bronchoscopic radio-frequent ablation of the parasympathetic pulmonary nerves in patients. In this technique called targeted lung denervation, energy is delivered via a dual-cooled radiofrequency catheter (Holaira, Inc., Minneapolis, MN, USA) designed to target tissue heating at a certain depth thereby ablating nerves around the main bronchi while minimizing effects to the inner surface of the airway. The first results showed that the targeted lung denervation treatment was feasible, safe, and potentially clinically effective. The improvements in spirometry appear durable, dose dependent and potentially additive to inhaled anticholinergic.[24] Further investigation is needed to evaluate procedural safety and performance of the Holaira System. A randomized sham controlled trial would be ideal to investigate the treatment effects of targeted lung denervation. Currently, further product development in a feasibility trial to establish the optimal energy level are underway (ClinicalTrials.gov NCT02058459).

References

1. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302-8.

2. Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomized controlled trial. Lancet 2015;386:1066-73.

3. Gompelmann D, Herth FJ, Slebos DJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration 2014;87:485-91.

4. Valipour A, Slebos DJ, de Oliveira HG, et al. Expert statement: pneumothorax associated with endoscopic valve therapy for emphysema-potential mechanisms, treatment algorithm, and case examples. Respiration 2014;87:513-21.

5. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-44.

6. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012;39:1334-42.

7. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302-8.

8. Venuta F, Anile M, Diso D, et al. Long-term follow-up after bronchoscopic lung volume reduction in patients with emphysema. Eur Respir J 2012;39:1084-9.

9. Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. Eur Respir J 2011;37:1346-51.

10. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059-73.

11. Shah PL, Slebos DJ, Cardoso PF, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomized, sham-controlled, multicentre trial. Lancet 2011;378:997-1005.

12. Slebos DJ, Hartman JE, Klooster K, et al. Bronchoscopic Coil Treatment for Patients with Severe Emphysema: A Meta-Analysis. Respiration 2015;90:136-45.

13. Stoller JK, Gildea TR, Ries AL, Meli YM, Karafa MT, National Emphysema Treatment Trial Research Group. Lung volume reduction surgery in patients with emphysema and alpha-1 antitrypsin deficiency. Ann Thorac Surg 2007;83:241-51.

14. Mahler DA, Faryniarz K, Tomlinson D, et al. Impact of dyspnea and physiologic function on general health status in patients with chronic obstructive pulmonary disease. Chest 1992;102:395-401.

15. Deslee G, Mal H, Dutau H, et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. JAMA 2016;315:175-84.

16. Schuhmann M, Raffy P, Yin Y, et al. Computed tomography predictors of response to endobronchial valve lung reduction treatment. Comparison with Chartis. Am J Respir Crit Care Med 2015;191:767-74.

17. Klooster K, Ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med 2015;373:2325-35.

18. Fuehner T, Clajus C, Fuge J, et al. Lung Transplantation after Endoscopic Lung Volume Reduction. Respiration 2015;90:243-50.

19. Dejene S, Ahmed F, Jack K, Anthony A. Pneumothorax, music and balloons: A case series. Ann Thorac Med 2013;8:176-8.

20. Herzog D, Poellinger A, Doellinger F, et al. Modifying Post-Operative Medical Care after EBV Implant May Reduce Pneumothorax Incidence. PloS One 2015;10(5):e0128097.

21. Zoumot Z, Kemp SV, Caneja C, Singh S, Shah PL. Bronchoscopic intrabullous autologous blood instillation: a novel approach for the treatment of giant bullae. Ann Thorac Surg 2013;96:1488-91.

22. Manley K, Coonar A, Wells F, Scarci M. Blood patch for persistent air leak: a review of the current literature. Curr Opin Pulm Med 2012;18:333-8.

23. Mizumori Y, Mochiduki Y, Nakahara Y, et al. Effects of bronchoscopic lung volume reduction using transbronchial infusion of autologous blood and thrombin in patients with severe chronic obstructive pulmonary disease. J Thorac Dis 2015;7:413-21.

24. Slebos DJ, Klooster K, Koegelenberg CF, et al. Targeted lung denervation for moderate to severe COPD: a pilot study. Thorax 2015;70:411-9.