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Endoscopic Lung Volume Reduction

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1. Introduction

Chronic obstructive pulmonary disease (COPD) that presents a growing cause for mortality worldwide [1, 2] is characterized by chronic bronchitis, obstructive bronchiolitis and emphysema. The most important etiologic factor is cigarette smoking, but occupational and environmental dusts as well as genetic factors contribute to COPD developing. The exposure to these noxious inhaled agents lead to abnormal pathogenic reactions like a permanent airway inflammation, imbalance between proteinases and antiproteinases, impairment of elastin repair and increased oxidative stress with subsequent lung parenchyma destruction [3]. The progressive permanent enlargement of airspaces distal to terminal bronchioles results in a decrease in lung elastic recoil, air trapping and hyperinflation, thus leading to airflow limitation and increased residual volume. These alterations of respiratory mechanics cause the symptoms of dyspnoea, limited exercise capacitiy and reduced quality of life. Therapeutic recommendations for COPD consisting of bronchodilators, glucocorticosteroids, long term oxygen therapy and rehabilitation are common insufficient in advanced COPD [4]. Therefore, surgical treatments like Lung Volume Reduction Surgery (LVRS) and lung transplantation should be considered in advanced disease. The resection of emphysematous lung tissue results in improvement of lung elastic recoil with subsequent increased expiratory flow. Furthermore, the reduction of hyperinflation allows the diaphragm to function more effectively and increases the global inspiratory muscle strength [5].

Already in the 1950s, the first lung volume reduction surgery has been performed to achieve lung volume reduction with subsequent improvement of respiratory mechanics leading to decreased breathlessness on exertion and increased exercise capacity. Although a physiological improvement could be observed, the surgical treatment did not attract attention due to high perioperative mortality [6]. Just in the 1990s the surgical treatment was reintroduced and the positive results have been confirmed in several trials [7-10]. The most known trial related to LVRS is the multicenter “National Emphysema Treatment Trial” (NETT) [10] comparing the surgical treatment to standard medical care in 1.218 patients with severe emphysema. The results of NETT showed that patients with predominantly upper lobe emphysema experienced significant improvement in clinical outcome measurements. However, the 90-day mortality rate in the surgery group was 7.9% and thus significant higher than in the medical-therapy group. Particularly, in patients with non upper lobe predominant emphysema and poor lung function, a high mortality could be

observed. Therefore, different bronchoscopic approaches have been developed imitating the LVRS but with less morbidity and mortality.

Until now, there are various techniques of Endoscopic Lung VolumeReduction (ELVR) extending the therapeutic strategies in patients withsevere emphysema. In general, reversible blocking techniques and irreversible, non-blocking techniques can be distinguished. The application of these different techniques is dependent on the emphysema distribution and degree of collateral ventilation. Therefore, an accurate patient selection has great importance.

2. Reversible, blocking techniques

The first and most known method of endoscopic lung volume reduction is the implantation of valves in targeted most destroyed lung compartments in patients with heterogeneous emphysema [11]. These blocking devices allow the air to be expelled during expiration but prevent the air entering the target lobe during inspiration and so facilitating atelectasis to achieve lung volume reduction. Two different valves are available: endobronchial valves (EBV, Zephyr ®, Pulmonx, Inc., Palo Alto, Calif., USA) and intrabronchial valves (IBV, Spiration®, Olympus Medical Co., Tokio, Japan).

2.1 Implantation technique

The endobronchial (figure 1) and intrabronchial valves (figure 2) only differentiate in shape, but the implantation technique and their functional principle is very similar. The endobronchial valves consist of a cylindrical nitinol framework, whereas the intrabonchial valves have got an umbrella shaped nitinol skeleton. Both valves are covered by a silicone membrane. Endobronchial valves are available in two different sizes, intrabronchial valves in three different sizes. Prior to valve implantation, the diameter of the bronchus that is considered to be blocked by the valves is estimated by using the measurement wings of the delivery system or a special balloon catheter. Afterwards, the appropriately sized valves are preloaded in a delivery catheter that can be introduced through a 2.8 mm or larger working channel of a standard flexible bronchoscope. The catheter is placed in the airway of the target lobe and by retracting the sheath, the valve can be deployed easily that expanded against the bronchial wall. The procedure can be performed under general anesthesia as well as under conscious sedation and takes generally 10 to 30 minutes depending on the number of valves that are placed.

2.2 Endobronchial valves (EBV)

The first published trials related to endoscopic lung volume reduction by valves were about the implantation of EBV in patients with severe heterogeneous emphysema by Toma et al. and Snell et al. in 2003 [12; 13]. Since then, several series have been published [14; 15]. The biggest and most noted trail however is the "Endobronchial Valve for Emphysema Palliation Trial" (VENT) that has been published by Sciurba et al. in 2007 [16]. In this prospective trial, 321 patients with severe emphysema were randomly assigned in a 2:1 ratio to receive endobronchial valve treatment or standard medical care. 6 months following the treatment, the results referring to the lung function test revealed a mean between group-difference of 6.8% in FEV_1.

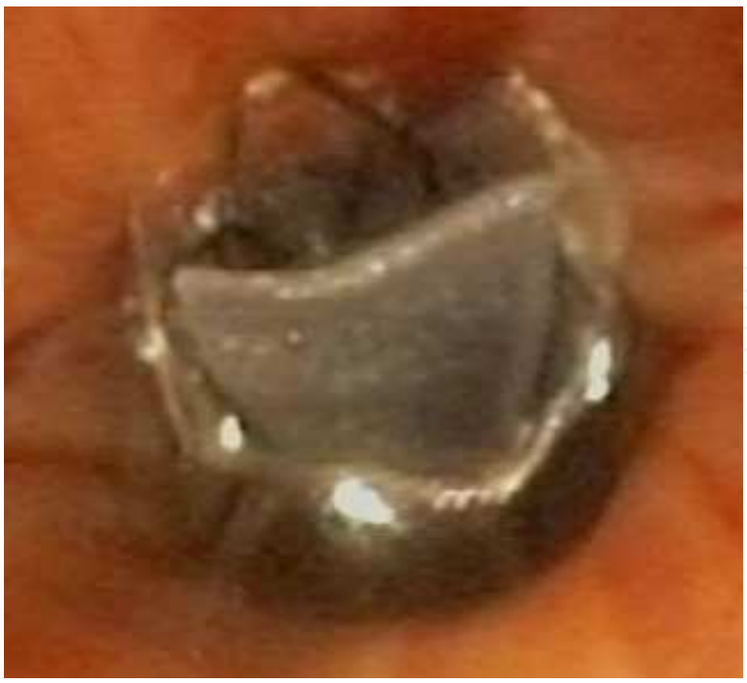


Fig. 1. Endobronchial valve.

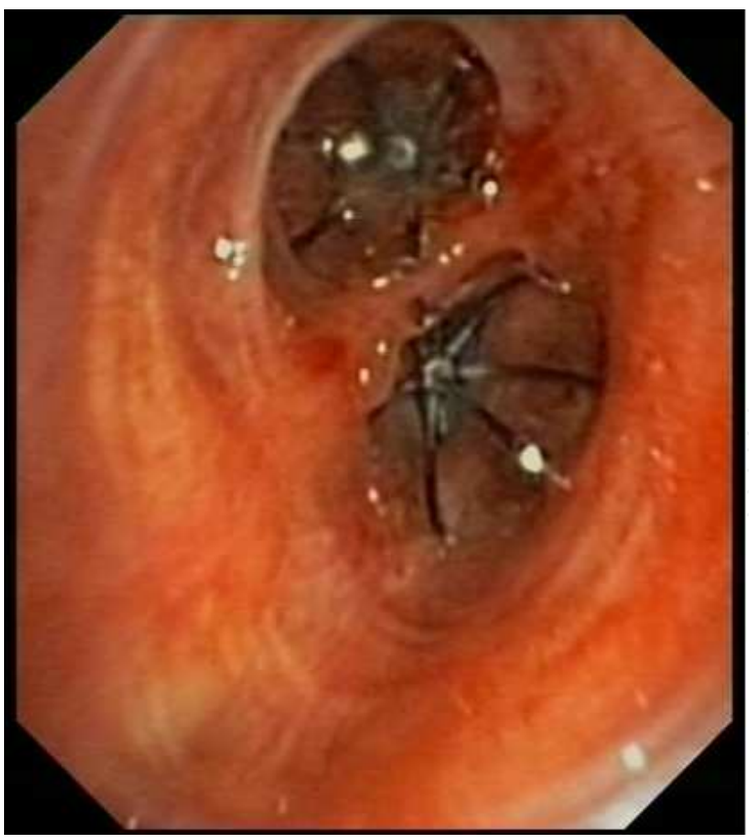


Fig. 2. Intrabronchial valve.

Furthermore, a mean between-group difference of 5.8% in the 6-minute-walk distance could be detected. Among the patients who received EBV, there was a greater reduction in the lung volume of the target lobe measured by high-resolution computed tomography (HRCT). At 12 months, the complication rate was 10.3% in the EBV group versus 4.2% in the control group. Some predictive characteristics were observed in sub analysis of this study. The beneficial effects were greatest in patients with presence of high heterogeneity of their emphysema distribution and an accurate lobar exclusion by the valves. Furthermore, interlobar fissure integrity that was analyzed as a surrogate for collateral ventilation (CV) in the computed tomography has also been observed as an independent predictor of treatment response. Therefore it is thought that CV is one of the most relevant factors responsible for valve therapy failure. Nowadays, there are two different options to predict the CV and thus the success of valve treatment. On the one hand, fissure integrity can be assessed in the HRCT, on the other hand, a catheter-based endobronchial approach providing quantitatively measurement of collateral resistance has been proposed (figure 3). In one double-blind prospective study in 2010 evaluating the safety and feasibility of this catheter-based system 25 patients with heterogeneous emphysema underwent the endobronchial determination of collateral resistance by using the catheter-based system followed by an EBV treatment [17]. In all patients, the resistance measurement was safely and successfully achieved. A correlation of the measurements with the event of atelectasis after ELVR was found in 90% of the analyzable cases. In a following multicenter study covering patients with severe heterogeneous upper lobe or lower lobe predominant emphysema, the accuracy of this catheter-based system in correctly predicting the target lobe volume reduction was evaluated [18]. Following the CV measurement by using the catheter-based system a complete occlusion of the target lobe by EBV was performed. The target lobe volume reduction after the valve implantation was assessed by HRCT 30 days following the intervention. Out of 80 patients, CV assessment prospectively showed a low CV in 51 patients and a high CV in 29 patients. The accuracy of the catheter-based system in correctly predicting the target lobe volume reduction was found to be 75%. Therefore, this quantitatively measurement of collateral ventilation predicts of whether endoscopic lung volume reduction would be successfully or not.

2.3 Intrabronchial valves (IBV)

There are also several published trials confirming the efficacy of the treatment with intrabronchial valves in patients with heterogeneous emphysema. In most of these studies a bilateral incomplete occlusion of both lobes in patients with upper lobe predominant emphysema was performed to minimize the risk of pneumothorax. The results showed an improvement in health-related quality of life and regional lung volume changes measured by quantitative and qualitative analysis of HRCT [19; 20; 21]. However, in all these studies no significant change in lung function test or 6-minute-walk test could be observed. Therefore, it is thought, that bilateral partial closure leads to redistribution of ventilation but avoid atelectasis with subsequent absence of improvement of these objective clinical outcome measures. To evaluate this hypothesis, a randomized prospective study comparing unilateral complete versus bilateral incomplete endoscopic lung volume reduction by IBV implantation in 20 patients with severe upper lobe predominant emphysema was performed

[22]. The results demonstrated a greater benefit in patients receiving the unilateral endoscopic lung volume reduction with complete occlusion of one lobe. Significant differences were evaluated in FEV_1 (+32.5% vs. +2.5%) as well as in the 6-minute-walk test (+43m vs. -19m). In conclusion, unilateral treatment with complete occlusion appears superior to bilateral incomplete treatment but with higher risk of pneumothorax.

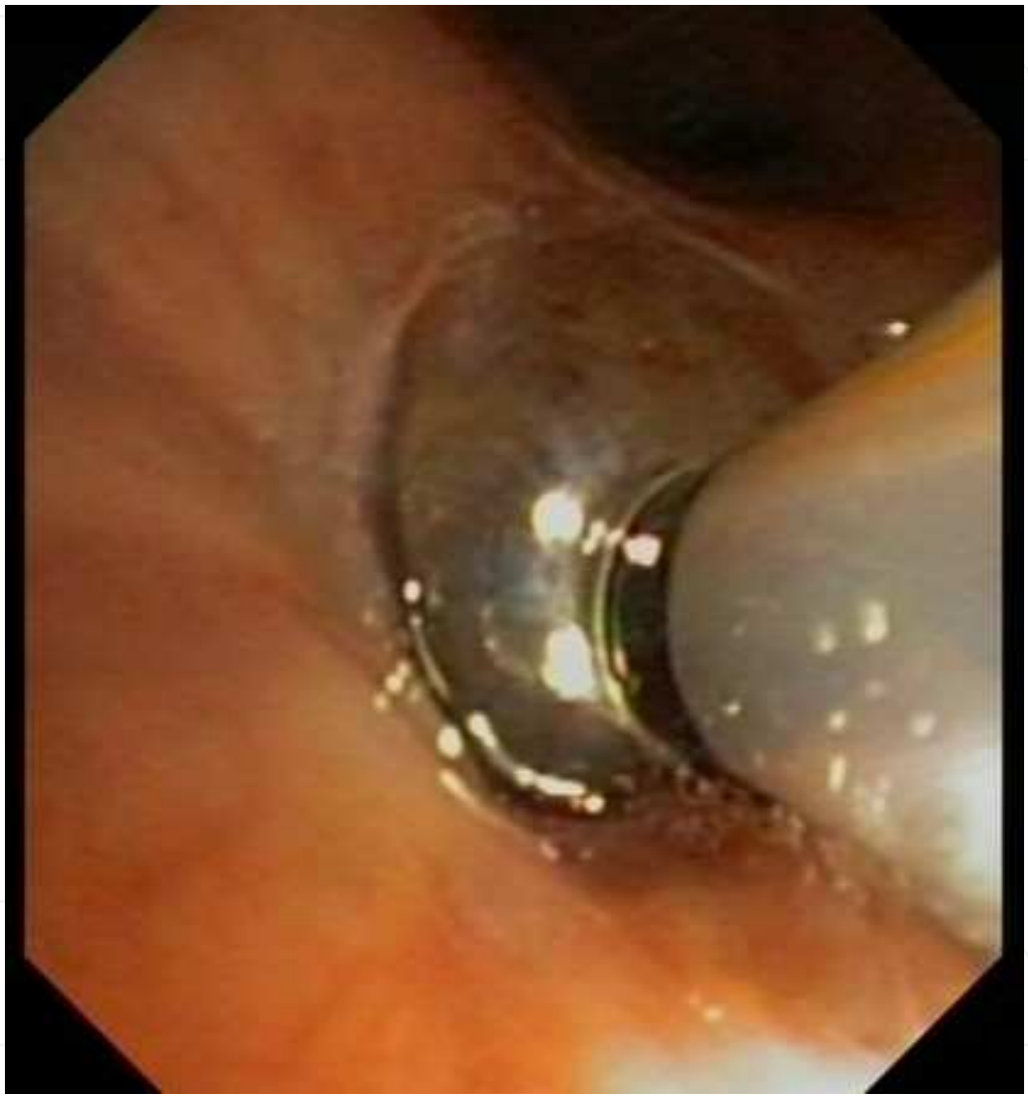


Fig. 3. Catheter-based measurement of collateral ventilation. At the tip of the catheter, there is a balloon, that is be inflated within the airway to isolate the target lobe. The air is directed through the catheter to the console for measurement of air flow and air pressure.

3. Irreversible, non-blocking techniques

Besides the blocking devices, there are various non-blocking techniques for bronchoscopic emphysema therapy. Implantation of lung volume reduction coils, polymeric lung volume reduction, bronchoscopic thermal vapour ablation and creation of airway bypasses can be

distinguished. These techniques seem to be independent of collateral ventilation, however these methods are irreversible.

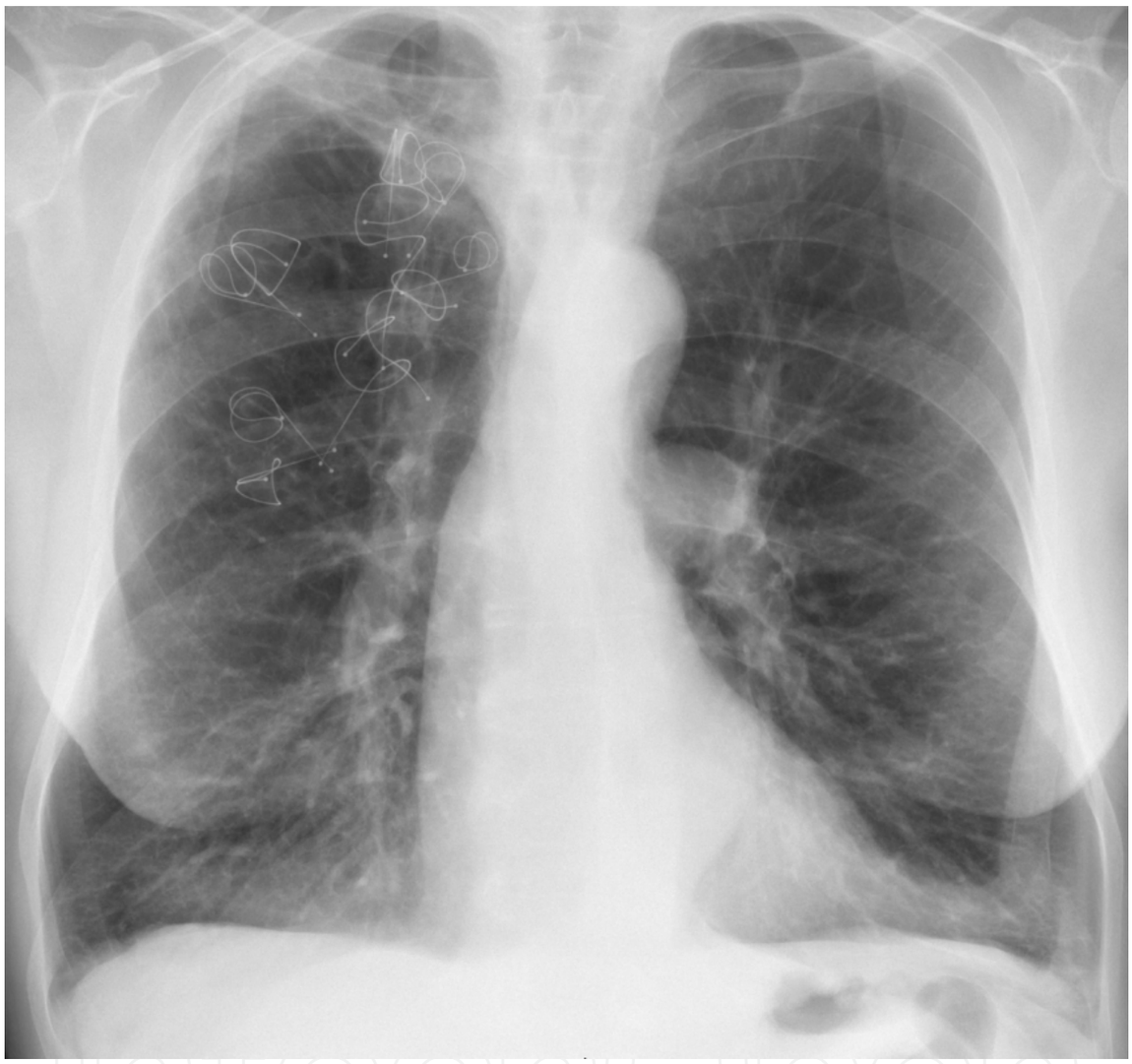


Fig. 4. Chest x-ray following the implantation of lung volume reduction coils in the right upper lobe. In courtesy of Prof. Dr. med. CP Heussel, Thoraxklinik Heidelberg.

3.1 Lung Volume Reduction Coils (LVRC)

One of these non-blocking endoscopic techniques is the implantation of lung volume reduction coils (LVRC, PneumRx, Inc., Mountain View, Calif., USA). These coils consisting of a nitinol wire have got a preformed shape that results in parenchymal compression and thus achieving a lung volume reduction. For implantation, the airway is identified bronchoscopically. Afterwards a low stiffness guidewire is advanced into the airway under fluoroscopic guidance with a distance of 15 mm between the distal end of the guidewire and the pleura. Next, a catheter is passed over the guidewire. Then the guidewire is removed and a straightened LVRC is introduced. As the catheter is pulled back, the coil assumes its

preformed shape leading to parenchymal compression. Figure 4 shows a chest x-ray following implantation of coils in the right upper lobe. In a pilot study using coils in heterogeneous as well as in homogeneous emphysema, the patients with predominant heterogeneous disease appeared to show more substantial improvements in pulmonary function, lung volumes, 6 minute walk test and quality of life measures than patients with homogeneous disease [23]. According to these results, a study investigating the efficacy of LVRC treatment in 16 patients with only severe heterogeneous emphysema was performed [24]. 12 patients were treated bilaterally, 4 patients underwent treatment in one lobe. A median of 10 coils per lobe were placed. LVRC treatment in all patients resulted in significant improvements in pulmonary function, exercise capacity and quality of life, with an acceptable safety.

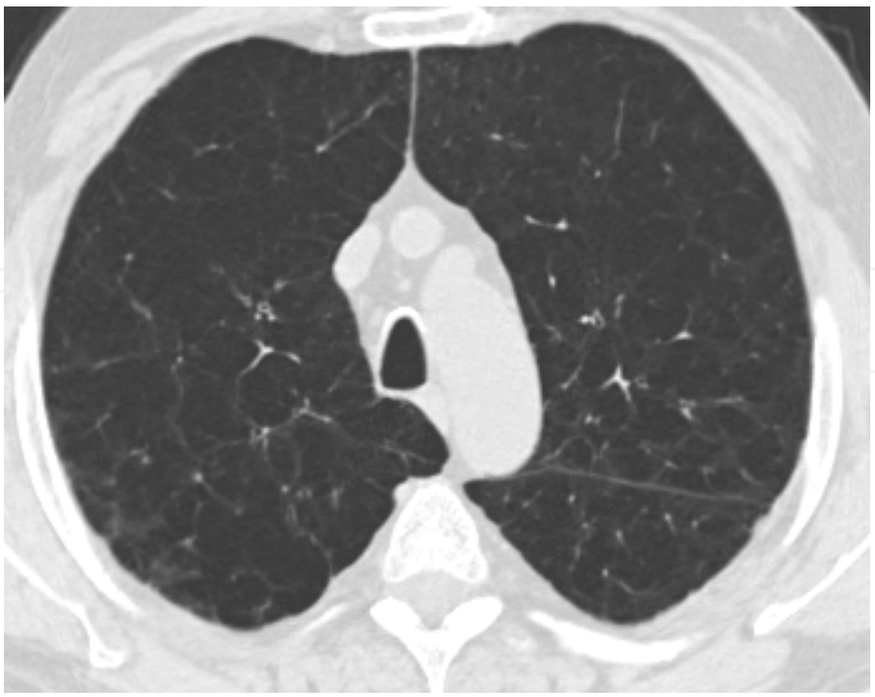
3.2 Polymeric Lung Volume Reduction (PLVR)

Polymeric lung volume reduction (PLVR, Aeris therapeutics, Inc. Woburn, Mass., USA) consists of administration of a foam sealant in the destroyed lung compartment resulting in local inflammatory reaction. This inflammation leads to fibrosis and scarring with subsequent lung volume reduction (figure 5a and 5b). PLVR can be offered to patients with heterogeneous disease, but also patients with homogeneous disease experience improvement after PLVR. However, further trials evaluating the efficacy of PLVR in patients with severe homogeneous emphysema are needed.

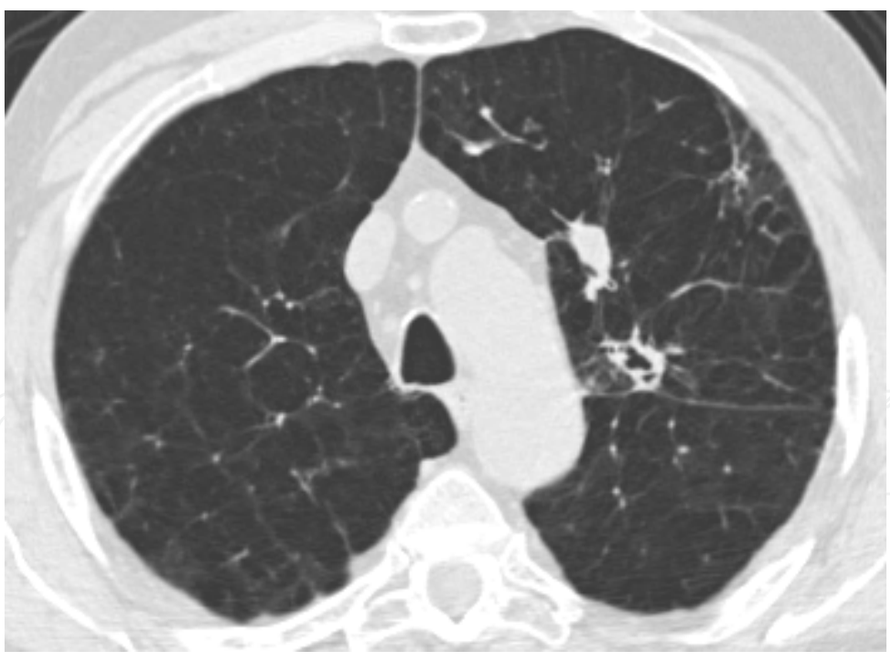
The sealant is administered via a special single lumen catheter that is inserted through the working channel of a standard flexible bronchoscope until its tip extends approximately 4 cm from the tip of the scope. During the administration of the sealant, the bronchoscope is maintained in wedge position preventing backflow of the sealant at the airway subsegment. The injection time of the sealant that is prepared in a syringe takes about 10-20 seconds. The bronchoscope should be maintained in wedge position for one minute following delivery to allow complete in situ polymerization. Afterwards, the bronchoscope is repositioned at the next subsegment and the procedure is repeated [25].

The first studies related to PLVR showed encouraging results with beneficial effects in selected patients with heterogeneous emphysema [26; 27] as well as with homogeneous emphysema [28]. Furthermore, a multicenter dose-ranging study revealed, that patients who received high dose treatment with 20 ml per subsegment experienced greater improvement in clinical outcomes than patients with a low dose treatment with 10 ml per subsegment [27]. In these trials, biological reagents were instillated to initiate an inflammatory reaction and a collapse of targeted lung portions, but it then was replaced by synthetic AeriSeal foam that allows a simpler production without blood products.

In one recently published multicenter trial, 25 patients with severe upper lobe predominant emphysema underwent PLVR by using AeriSeal foam [29]. All patients tolerated the treatment without significant adverse events. However, a flu-like reaction following the procedure could be detected in all patients. 24 weeks after the PLVR, physiological and clinical benefits were observed. Furthermore, efficacy responses were better among the patients with COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage III than among patients with COPD GOLD stage IV.



(a)

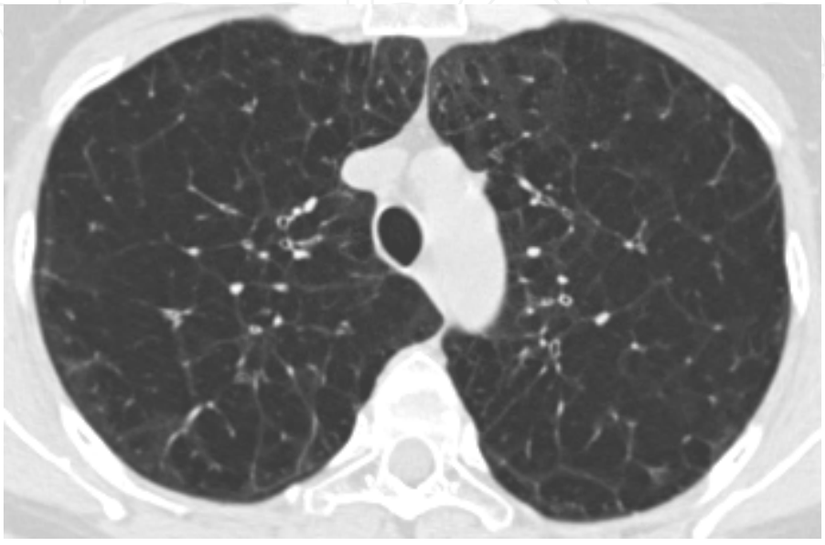


(b)

Fig. 5. Computed tomography acquired prior to polymeric lung volume reduction (a) in the left upper lobe and matched CT scan (b) taken 6 months following the treatment. The shift of the interlobar fissure shows the target lobe volume reduction. In courtesy of Prof. Dr. med. CP Heussel, Thoraxklinik Heidelberg.

3.3 Bronchoscopic Thermal Vapor Ablation (BTVA)

Bronchoscopic thermal vapor ablation (BTVA, Uptake Medical, Seattle, Wash., USA) is an alternative method that is very similar to PLVR. This technique consists of a vapor generator and a special InterVapor catheter used to deliver heated water vapor bronchoscopically to the most destroyed lung regions. The vapor induces an inflammatory reaction with subsequent fibrosis and scarring leading to lung volume reduction (figure 6a and 6b).



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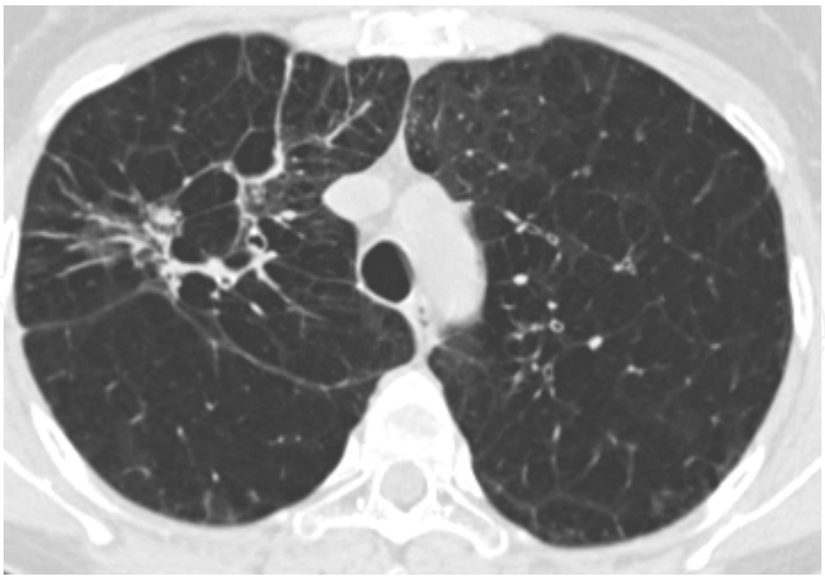

(b)

Fig. 6. Computed tomography taken prior to bronchoscopic thermal vapor ablation (a) in the right upper lobe. 6 months following the treatment a lobar volume reduction can be observed (b). In courtesy of Prof. Dr. med. CP Heussel, Thoraxklinik Heidelberg.

After identifying the target airway bronchoscopically, the InterVapor catheter is introduced through the working channel of the flexible bronchoscope. At the tip of the catheter there is a balloon that can be inflated within the airway so that the target lung region is isolated. Next, a predetermined dose of 125° C heated water vapor is delivered via the special InterVapor catheter.

In a 2009 reported study, 11 patients with heterogeneous emphysema treated by unilateral BTVA confirmed the feasibility and an acceptable safety profile [30]. Furthermore, an improvement of health-related quality of life could be observed. A recently published multinational single arm study evaluated the efficacy of the bronchoscopic thermal vapor ablation in 44 patients with upper lobe predominant emphysema. 24 patients received BTVA in the right upper lobe, 20 patients were treated in the left upper lobe in a single procedure with a target vapor dose of 10 cal/g. During the procedure, no adverse events could be observed. The most common adverse events following the treatment were COPD exacerbations, pneumonia and haemoptysis. 6 months following the treatment, efficacy data showed a 48% reduction of treated lobar volume assessed by HRCT measurement. Furthermore, the patients experienced significant improvement in lung function, exercise capacity and health-related quality of life [31].

3.4 Airway bypass

The creation of extra-anatomic passageways through the normal bronchial wall allowing the trapped air to escape presents a method of endoscopic lung volume reduction in patients with severe homogeneous emphysema (EASE, Broncus Technologies, Inc. Mountain View, USA).

The procedure is performed by using a standard flexible bronchoscope. After identifying the appropriate airway, a Doppler probe is used to confirm the absence of vessels behind the airway wall. Afterwards, the wall is punctured by a transbronchial needle. A balloon catheter is advanced into this hole and the balloon is inflated to enlarge the hole. After repeated confirmation of absence of vessels, a drug-eluting stent (DES) is placed to keep the bypass open over time. The trapped air can escape by bypassing the small airways leading to a lung volume reduction.

In one large prospective, sham-controlled study - EASE trial (Exhale Airway Stents for Emphysema) - 315 patients with severe homogeneous emphysema were subdivided into two groups [32]: only 208 patients out of the 315 patients received the airway bypasses. Immediately post procedure, reductions in lung volume could be evaluated demonstrating proof of concept for airway bypass. However, for the overall group, the initial benefit decreases by 6 months so that at least no sustainable benefit could be recorded with airway bypass in the patients with homogeneous emphysema. The most probable cause for loss of initial benefit is stent occlusion by mucus. Therefore, improvement of durability is required before airway bypasses could be recommend as beneficial therapy.

4. Patient selection

An accurate patient selection is the most important and most difficult issue in the area of endoscopic lung volume reduction. The various approaches require different conditions that must be fulfilled to achieve beneficial outcome. Therefore a treatment algorithm is necessary for identifying the best candidates for the different techniques of endoscopic lung volume reduction.

Patients with severe emphysema have to undergo a screening basic examination programme including lung function testing (spirometry, bodyplethysmography, diffusing capacity measurements), blood gases and exercise tests (6-minute-walk test). Electrocardiogramm, echocardiogram, chest x-ray as well as laboratory testing provide to evaluate patient´s clinical status prior to bronchoscopic intervention. To determine the emphysema distribution as well as fissure integrity, high resolution computed tomography scan at full inspiration and perfusion scan are necessary. Different visual scoring systems e.g. YACTA®, Pulmo® or Volume® can be used for detailed quantitative emphysema analysis. As alternative method to fissure analysis by HRCT, the catheter-based measurement can be performed to evaluate the degree of collateral ventilation.

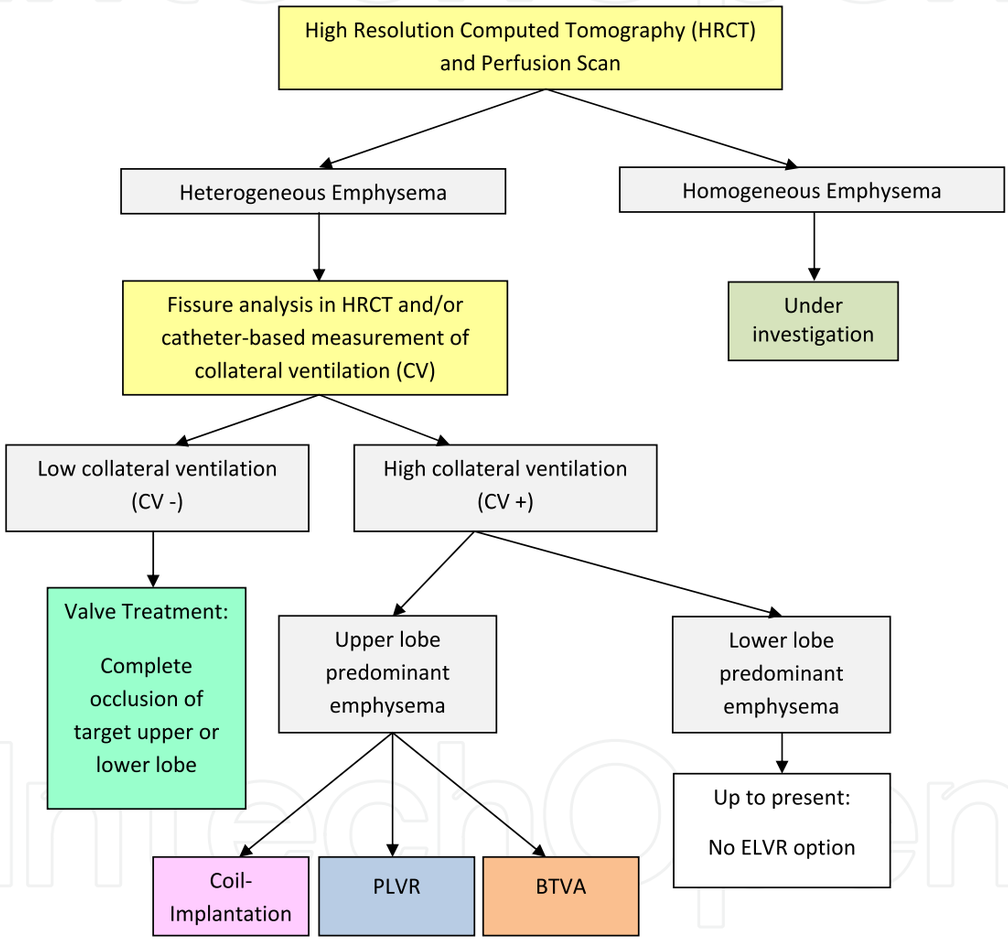

Fig. 7. Patient selection and therapy algorithm.

According to the VENT, following inclusion criteria should be fulfilled: forced expiratory volume in 1 s (FEV_1) < 45%, total lung capacity (TLC) > 100%, residual volume (RV) > 150 %, a partial pressure of arterial carbon dioxide of 50 mm Hg or less, a partial pressure of arterial oxygen of at least 45 mm Hg (without oxygen therapy), a 6-minute-walk distance of > 140 m. Greatest beneficial effects can be observed in patients with a severe hyperinflation with a RV > 200% and a high RV/TLC. Depending on the emphysema distribution and the fissure integrity, the method of endoscopic lung volume reduction is chosen (see figure 1).

5. Complications

5.1 Valve Implantation

The most common adverse event following valve implantation is pneumonia distal the valves despite the valves allow secretion to pass. The VENT revealed a pneumonia rate of 4.2% [16]. In 1/3 of these cases, valve removal was necessary for recovery. In very rare cases, development of bronchiectasis can be observed distal the valves requiring valve removal. Another frequent risk is pneumothorax after valve treatment. Therefore, pneumothorax must be ruled out by chest x-ray 2 hours and 24 h following the intervention. Pneumothorax occurs particularly in patients who experience a great improvement in clinical outcome following valve placement due to a rapid atelectasis. Chest tube drainage is required in some patients with lung collapse. In case of persistent fistula, the removal of one of the implanted valves provides lung expanding and thus sealing fistula. Surgical intervention is only needed to treat fistula that remains persistent despite of adequate chest tube drainage and valve removal. Development of granulation tissue formation that is often associated with bleeding complication is another side effect related to valves due to the pressure of the valves on the mucosa. Cryotherapy is recommended for the treatment of severe granulation tissue formation. New or worsening hypercapnia is another adverse event. Therefore, repeated blood gas analysis following the valve implantation is required. Only in few cases non-invasive ventilation and/or valve removal is necessary. COPD exacerbation, mild haemoptysis, chest pain and valve migration are other anticipated complications to valve treatment.

5.2 Coil Implantation

Side effects rated as possibly related to either the procedure or the device are haemoptysis, dyspnoea, cough, COPD exacerbations, peumonia and chest pain. Pneumothorax can also occur following coil implantation. To minimize risk of pneumothorax, a distance of at least 15 mm to pleura should be kept.

5.3 Polymeric Lung Volume Reduction and Bronchoscopic Thermal Vapor Ablation

The effect of PLVR and BTVA is based on an inflammatory reaction that results in fibrosis, scarring and shrinking. Due to this inflammation, the majority of the patients experience a "flu-like" reaction with dyspnoea, transient fever, pleuritic chest pain, leucocytosis, elevated C-reactive protein and infiltration in chest x-ray. This inflammatory response is self-limiting and resolves within 24-96 h with supportive care. Especially, systemic application of glucocorticosteroids is useful to diminish the symptoms following PLVR. Furthermore, a 7-day course of antibiotic prophylaxis for one week is required in each patient. Other adverse effects following PLVR and BTVA include COPD exacerbation, pneumonia, bronchitis or haemoptysis.

6. Conclusion

Endoscopic lung volume reduction presents an encouraging therapy modality for patients with advanced emphysema. However, efficacy depends strictly on patient selection requiring an appropriate diagnostic and treatment algorithm for identifying the best candidates for each of the various ELVR techniques. Complete lobar occlusion by valve implantation provides an effective option for patients with severe heterogeneous upper lobe

or lower lobe predominant emphysema and low collateral ventilation. Irreversible, non-blocking techniques that seem to be independent of collateral ventilation are minimally invasive endoscopic approaches for patients with upper lobe predominant emphysema.

7. References

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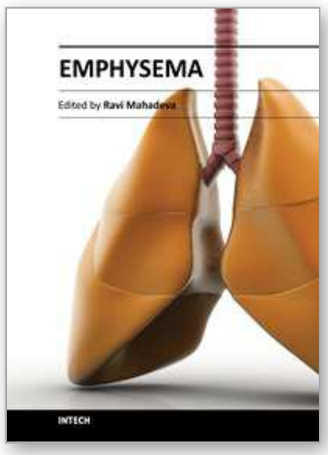

Emphysema

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Chronic Obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality world-wide. The most common cause is chronic cigarette smoke inhalation which results in a chronic progressive debilitating lung disease with systemic involvement. COPD poses considerable challenges to health care resources, both in the chronic phase and as a result of acute exacerbations which can often require hospital admission. At the current time it is vital that scientific resources are channeled towards understanding the pathogenesis and natural history of the disease, to direct new treatment strategies for rigorous evaluation. This book encompasses some emerging concepts and new treatment modalities which hopefully will lead to better outcomes for this devastating disease.

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