INTRODUCTION

Emphysema is a progressive, debilitating disease that is characterized by destruction of lung tissue as a result of inflammation caused in most patients by exposure to noxious inhaled agents for extended periods. The most common cause of this condition is cigarette smoking, although genetic, occupational, and environmental causes account for up to 10% of cases (1). Despite aggressive public health initiatives aimed at discouraging the use of cigarettes, smoking-related lung diseases remain a significant cause of disability and death worldwide. Due to the number of current and new smokers, emphysema is expected to remain a leading cause of morbidity and mortality for many years to come (2).

Emphysema is unique among the chronic obstructive pulmonary diseases (COPD) in that it involves irreversible destruction of alveolar tissue. By contrast, other forms of COPD (asthma and chronic bronchitis) primarily affect the airways. In emphysema, the tissue damage, which is caused by chronic inflammation, eventually results in a decrease in lung elastic recoil, progressive hyperinflation and gas trapping due to premature closure of small airways. Consequently, the lung becomes too large to fully expand and function effectively within the rigid chest cavity. Exercise capacity is reduced since the ability to take deep breaths is compromised. The respiratory muscles are forced to function at a mechanical disadvantage and work of breathing is increased. Patients experience chronic shortness of breath, limited exercise capacity and reduced quality of life. Because the principal defect in emphysema is hyperinflation due to destruction of elastic tissue, conventional medical treatment consisting of bronchodilator and anti-inflammatory medications is generally of limited benefit (1,3).

Surgical treatments for emphysema, including lung volume reduction surgery (LVRS) and lung transplantation, have been used to treat patients with advanced disease. Damaged areas of lung are resected to increase breathing capacity and reduce lung hyperinflation. Whether performed via median sternotomy or less invasive video-assisted thoracoscopy, LVRS involves major thoracic surgery in a generally elderly population with limited breathing capacities that frequently have clinically significant co-morbid conditions. LVRS has proven beneficial for selected patients, since it directly addresses the problem of lung hyperinflation through resection of damaged tissue (4-6). By restoring a more normal relationship between the lung and chest wall, volume reduction therapy reduces gas trapping, improves elastic recoil, increases expiratory flows, and allows the rib cage and diaphragm to function more effectively. Clinically, this results in decreased symptoms of dyspnea, improved exercise capacity, and an overall improvement in quality of life. The benefits of lung volume reduction through surgical resection have been confirmed in single center studies, and in the multi-center National Emphysema Treatment Trial (NETT), a 1218 patient randomized controlled clinical trial performed at 17 centers across the United States (7).

NETT demonstrated that a selected subset of patients randomized to LVRS experienced significant improvements in lung function, exercise capacity and quality of life. However, NETT also revealed that LVRS is associated with a high incidence of serious cardiopulmonary compli-
cations, and does not benefit all patients with advanced emphysema (8, 9). Fifty nine% of patients enrolled in NETT experienced significant cardiac or respiratory complications within the first 30 days after surgery. Furthermore, some patients with advanced emphysema had worse outcomes with surgery. Patients with marked reductions in FEV1 (<20% predicted) and either homogeneous disease or reduced diffusing capacity (< 20% predicted) experience a statistically significant increase in 90-day mortality following LVRS (10). Post-hoc analysis also revealed a trend towards increased mortality following LVRS in patients with non-upper lobe emphysema and high exercise capacity. Thus, despite its potential benefits fewer than 300 cases of LVRS are performed annually in the US and there are similarly small numbers in Europe (11).

The procedure is associated with substantial risk. The postoperative 3-month mortality is 5-10% and the non-lethal operative complication rate approaches 60%. The median length of hospital stay for LVRS is 10 days (range 8 to 14 days) in the US, 22 days (range 4 to 161 days) in Canada and 14.5 days (range 9 to 35 days) in Europe (12,13). Lung transplantation also improves pulmonary function, symptoms, functional capacity, and quality of life in patients with advanced emphysema, but is available to only approximately 2000 patients annually due to limited organ availability and access to specialized tertiary care centers. COPD has been the primary indication for transplantation in approximately 37% of patients undergoing operation (14). Although Single Lung transplantation remains the predominant surgical therapy for advanced COPD, the proportion of patients undergoing bilateral transplantation for COPD continues to increase (15).

Furthermore, transplantation often has no significant effect on overall mortality in emphysema. Chronic rejection remains a major unresolved problem among patients who undergo lung transplantation, and is associated with a 50% 5 year mortality (14).

Therefore, minimally invasive techniques have been proposed as a method to reduce lung volume in these patients without undergoing open thoracotomy. Different endoscopic LVR (ELVR) systems are undergoing evaluation to accomplish surgical LVRS without the concomitant surgical morbidity. Nowadays the techniques are different depending to the CT morphology of the emphysema subtype. For heterogeneous diseases reversible, blocking techniques are competing with non-blocking, reversible and non-blocking, irreversible options. The creation of a communication between segmental bronchi and emphysematous lung parenchyma is meant to offer an extra-anatomic means of expiratory air flow and focuses on patients with homogeneous emphysematous changes.

The aim of this thematic review is to give an overview about the techniques and the available data.

**BLOCKING, REVERSIBLE DEVICES**

**Pulmonx valve**

The greatest experience to date has been published on the Zephyr® (Pulmonx, Inc., Palo Alto, CA, USA) endobronchial valve (EBV). The implant is a silicone-based, one-way valve mounted on a nitinol stent (Figure 1). The intent of this device is to prevent air from entering the blocked segment while allowing the venting of expired gas and secretions, leading to atelectasis of the isolated emphysematous segments with subsequent reduction in lung volume (16). The valve is deployed through the working channel of a flexible bronchoscope and offers less resistance to expiratory flow than previous models. Toma and colleagues (17) published the first pilot study of unilateral volume reduction by endobronchial valve insertion. On average, 3.1 valves were placed in eight patients with a median FEV1 of 0.79 liters (24% predicted). After 4 weeks, FEV1 increased by 34% and the median DLCO by 29%. Upper lobe collapse was noted in 50% of the patients, and improvement in lung function was greatest in these patients with signs of collapse. Two patients developed an ipsilateral pneumothorax and three had exacerbations of their disease. Since then, different series have been published (18-20), followed by the results of a registry report on 98 patients treated with the Zephyr® valve (21). After 90 days of follow up, residual volume decreased by 4.9%, FEV1 increased by 11%, FVC increased by 9%, and six-minute-walk distance improved by 23%. Greater improvement was noted in unilateral LVRS, lobar exclu-

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**Figure 1.** 2 endobronchial valves placed in the left upper lobe
tion recipients, and patients with a baseline FEV1 less than 30% predicted or a residual volume (RV) greater than 225% predicted.

To prove the concept of the valves compared to LVRS a randomized prospective multicenter study of the safety and efficacy of unilateral treatment with endobronchial valves to improve lung function and exercise tolerance in advanced emphysema was performed (22).

The VENT (Endobronchial Valve for Emphysema PalliationN Trial) trial compared the safety and efficacy of Zephyr® endobronchial valves (EBV) in heterogeneous emphysema to best medical treatment, including pulmonary rehabilitation. High Resolution Computed Tomography (HRCT) images provided indices of disease severity, distribution and inter-lobar fissure integrity. Co-primary efficacy endpoints were percent changes (baseline to 6 months) in FEV1 and six minute walk (6MWT) by multiple-imputation, intent-to-treat analysis. 321 subjects were enrolled; 220 subjects were randomized to EBV; 101 to control. Mean difference between groups was 6.8% for FEV1 (P=0.002) and median difference was 5.8% for 6MWT (P=0.019) in favor of EBV. Completed cases in the high heterogeneity subgroup demonstrated 12.3% (6.5, 18.1) FEV1 and 13.2% (4.2, 22.2) 6MWT increases in favor of EBV (both P<0.001). Four secondary endpoints (SGRQ, mMRC, daily oxygen usage, and maximum cycle workload) and the composite BODE index also improved with EBV. In the high heterogeneity subgroup 40.0% of EBV subjects had 1 point increase in BODE compared to 18.6% of controls (OR 2.9, P=0.002). A major complication composite score (death; empyema; massive hemoptysis; pneumonia; persistent air leak or respiratory failure) at 12 months was 4.6% for controls vs. 10.3% for EBV subjects (P=0.17) (23).

Also, similar to LVRS, the lung function and clinical benefits were greatest in the presence of heterogeneous lung involvement such that following reduction of the more severely diseased lung units, expansion of the more viable less emphysematous non-treated lung results in more substantial improvements in lung mechanics. Subjects with high heterogeneity (≥15%) difference in quantitative emphysema between targeted and adjacent lobe had greater improvements following EBV treatment in both FEV1 and 6-MWT than subjects with lower heterogeneity. The greater proportion of subjects showing clinically important changes in the high heterogeneity subgroup supports the use of quantitative HRCT as an important tool in optimizing patient selection and assessing the clinical responses to lobar volume reduction interventions.

CT fissure completeness also emerged as an independent predictor of treatment response. Studies on excised human lungs identified major defects in interlobar fissures in 21 to 30% of oblique fissures and up to 88% of right horizontal fissures (24-27). In contrast to normal human lung, resistance across these collateral channels in emphysema is low relative to airway resistance (28-39). CT fissure completeness was included in the analysis based on a plausible association with these low resistance collateral channels between lobes, a feature likely to mitigate the volume reducing effect of lobar isolation (31-33) This premise seemed to prove true since fissure completeness correlates with the magnitude of lobar volume change. Attention to fissure completeness should allowed improved patient selection and targeting to minimize the mitigating effects of collateral flow on the clinical response to EBV.

**Spiration valve**

The Intrabronchial Valve (IBV: Spiration, Inc., Redmond, WA) is also an implantable device (Figure 2) designed to obstruct airflow into targeted segments of diseased emphysematous lung. It is designed as a one-way valve built on six nitinol struts covered by polyurethane in the shape of an umbrella to allow conformation and sealing to the airways with minimal pressure on the mucosa. The valve limits airflow into targeted Airways distal to the valve, but allows egress of trapped air and secretions. In a non-randomised pilot study of 28 patients followed for 6 months, improvement in the St. George’s Respiratory Questionnaire was seen with a mean change of 26.8 points from baseline (34). No physiologic parameters were noted to improve with this approach. Complications developed in 17% of the patients, with periprostural arrhythmia, bronchospasm, pneumonia, and COPD exacerbations occurring most frequently (35). No pneumothoraces were reported. Two trials on the system finished enrolment, a part of the data of the US trial were already published. In this multicenter study patients with severe
obstruction, hyperinflation and upper-lobe predominant emphysema were treated with bronchial valves placed bilaterally into upper-lobes (UL). Valve placements were possible in desired airways with 99.7% technical success with no migration or erosion. There were no procedure related deaths and 30 day morbidity and mortality were 5.5% and 1.1%. Pneumothorax was the most frequent serious device-related complication and primarily occurred when all the segments of a lobe, especially the left UL, were occluded. Highly significant health-related quality of life improvement in 55% of patients was observed at 6 months, but there was no randomised control group. HRQL improvement was associated with a decreased volume (mean -294 ml) in the treated lobes without visible atelectasis. Total lung volume was not changed due to a proportional shift of inspired volume to the untreated lobes. Combined with perfusion scan changes, this suggests that there is improved ventilation and perfusion matching in non-UL lung parenchyma.

**Mechanisms for success or failure**

Although atelectasis of emphysematous lung is the intended consequence of ELVR with blocking devices, pilot work has shown both that lobar collapse occurs relatively infrequently and that it is not necessary for clinically apparent benefit, suggesting that other physiological mechanisms must operate. It should be noted that this assessment can be technically difficult because the emphysematous destruction present makes accurate location of landmarks such as fissures problematic. The presence of collateral ventilation was first confirmed by Van Allen et al. (36), who observed that significant gas exchange and ventilation could occur distal to a complete bronchial obstruction, implying that there must be connections between obstructed and unobstructed lung. The process of alveolar destruction that occurs in emphysema leads to a destruction of normal lung architecture, with incomplete interlobar fissures more common in emphysematous than in normal lungs (37). With the Chartis™ system (Pulmonx, Inc., Palo Alto, CA, USA) a first technique to measure CV during a broncoscopy is possible. The Catheter is placed through the working channel of a bronchoscope. After the target lung segment is accessed by the bronchoscope, inflation of the balloon component on the distal tip seals the airway from airflow either in or out of the lung segment. Instead, air flows out of the target compartment into the environment only through the Catheter central lumen. Airway flow and pressure exiting the Catheter during spontaneous respiration is displayed in a graphic format. Functional assessment of air pressures and flows takes less than 5 minutes in the lung compartment isolated by the balloon (38). First available data of the system showed a high correlation between the measurement and presence of an atelectasis after ELVR with the Zephyr®r device (38).

**NON BLOCKING, REVERSIBLE DEVICES**

**Lung volume reduction coil (LVRC)**

The PneumRx Lung Volume Reduction Coils (PneumRx, Inc., Mountain View, CA, USA) are made from Nitinol wire that has been pre-formed to a shape that results in parenchymal compression after deployment (Figure 3). The coils are implanted bronchoscopically using a proprietary delivery system. First, the airway in the selected segment is identified bronchoscopically and a low stiffness guidewire is advanced into the airway under fluoroscopic guidance. A catheter is passed over the guidewire and the length of the airway is measured using radiopaque markers on the guidewire. The catheter is pulled back the LVRC assumes its pre-formed shape, pulling the airway and attached parenchyma with it. It is possible to remove or reposition the coil by reversing the implantation process. The most commonly used lengths are 100 and 125 mm. In a first trial Herth at al. (39) used the coils in eleven patients were treated. Of these 10 received a second treatment. A total of 33 adverse events were reported in 11 patients. Forty-two percent (14/33) of adverse events were deemed to be “not related” to the device or procedure and 58% (19/33) were “possibly related” to the device or procedure. None were deemed probably related to the device or procedure. Adverse events rated as possibly related to either the procedure or the device were dyspnea (10 events), cough (5 events), COPD exacerbation (3 events) and chest pain (1 event). No pneumothorax occurred. Although the study was neither intended nor powered to analyze effectiveness, some interesting trends have emerged. Although the mean changes over all patients in effectiveness endpoints...
were small, the group with predominantly heterogeneous disease appeared to show substantial improvements in pulmonary function, lung volumes, 6 minute walk tests and quality of life measures. Ongoing trials are focused to efficacy.

NON-BLOCKING, IRREVERSIBLE TECHNIQUES

Bronchoscopic thermal vapor ablation (BTVA)

The Bronchoscopic Thermal Vapor Ablation (BTVA) System (Uptake Medical, Seattle, WA, USA) is a minimally invasive bronchoscopic treatment aimed at inducing LVR in heterogeneous emphysematous patients. The potential benefits of this approach over other experimental approaches seems the independency of collateral ventilation. The system consists of a reusable Vapor Generator with a disposable bronchoscopic catheter, used to deliver heated water vapor bronchoscopically to targeted emphysematous lung regions. During the procedure, the Vapor Catheter is bronchoscopically introduced into the portion of airway selected for treatment, where a Vapor Catheter occlusion balloon is inflated and the predetermined vapor dose is delivered to the targeted lobar segment. The System delivers an endobronchial application of thermal energy to achieve targeted, complete, and permanent lung volume reduction. Success of the vapor-based BTVA is believed to be attributable to a number of factors. Application of thermal energy (or heat) causes an acute injury to the tissue, which then induces tissue repair with subsequent fibrosis and reductions in volume. The delivery of the thermal dose (along with modulation of the vapor temperatures and/or vapor application times) can also lead to other effects including, but not limited to, complete cell death and/or initiation of a healing process with new fibroblast growth and collagen deposition, all of which can induce the histological changes necessary to induce BTVA.

As with LVRS, BTVA creates space in the thoracic cavity (due to the volumetric reduction of non-viable emphysematous lung tissue) by reducing lung size, the remaining lung and surrounding muscles (intercostals and diaphragm) are able to work more efficiently. In a first trial by Herth et al. (40) patients underwent unilateral treatment. All had immediate mild X-ray opacification in the target area indicating a localized inflammatory response. Adverse events were exacerbation of COPD and hemoptysis. Two patients with COPD exacerbations have had prolonged hospital stays due to the pneumonia. All patients have experienced LVR and have completed D30 follow-up with a mean improvement in FEV₁ of 13.4%, VC of 6.3% and RV of 7.9%.

Early data on BTVA therapy confirms feasibility, an acceptable safety profile and the potential for efficacy. The efficacy results are anticipated to improve at the 3 and 6 month time points as healing and remodeling processes have matured.

Polymeric lung volume reduction (PLVR)

The Aeris Polymeric Lung Volume Reduction (PLVR) System (Aeris Therapeutics, Inc., Woburn, MA, USA) is a novel device system being developed for the treatment of advanced emphysema. PLVR therapy is administered bronchoscopically, and designed to provide the physiological benefits of lung volume reduction without the risks and cost of major surgery. Like LVRS, PLVR is proposed as a complement to medical therapy. The proposed mechanism through which PLVR produces it’s beneficial effects is the same as that of surgical lung volume reduction: by increasing lung recoil as a direct result of reducing lung hyperinflation. PLVR is designed to produce lung volume reduction non-surgically using a Hydrogel-Foam that flows into the damaged alveoli, adheres to the tissues, and produces lung volume reduction as the gas within the foam is absorbed, and the foam collapses. This reduces the size of hyperinflated regions of lung to produce therapeutic benefit.

The results of an open labeled, multicenter Phase 2 dose-ranging studies with PLVR Hydrogel administered to 8 subsegmental sites were presented at the European Respiratory Society meeting 2009 (41). It was shown, that PLVR improves physiology and functional outcomes up to 6 months with an acceptable safety profile in upper lobe predominant emphysema. Overall improvement was larger, and responses more durable with 20 mL/site than 10 mL/site dosage.

HOMOGENEOUS DISEASE

The airway bypass system

Airway Bypass (Broncus Technologies Inc., Mountain View, CA) is an investigational bronchoscopic procedure being studied to see if it can improve pulmonary function and dyspnea in patients with advanced homogeneous emphysema. During the procedure extra-anatomic pas sageways are created through the walls of the natural airways to connect the damaged lung parenchyma to the native airways. These new passages may provide a way for trapped air to escape by “bypassing” the collapsing small airways and at the same time giving access to the collaterally-ventilated tissue. After each new passage is made, a small drug-eluting stent is placed and provides support to keep the passageway open over time. Decreasing the volume of trapped gas might lead to an increase in inspiratory muscle strength, which could improve dyspnea, pulmonary function and quality of life.

Airway bypass is performed bronchoscopically using the Exhale® Doppler Probe, the Exhale® Transbronchial Dilation Needle and the Exhale Drug-Eluting Stent. All of these catheters fit down a 2 mm working channel. The procedure involves: 1) using the Doppler probe to scan the selected airway area, listening for sounds of blood flowing and identifying a quiet area away from blood vessels, 2) piercing the airway wall with the transbronchial needle, then...
retracting the needle, advancing the catheter and dilating the balloon to enlarge the hole, 3) rescanning the area around the newly-made extra-anatomic pathway with the Doppler probe to confirm the absence of surrounding blood vessels and 4) positioning the drug-eluting stent in the passageway and inflating the delivery catheter balloon to deploy it. The Exhale Drug-Eluting Stent is packaged on a balloon delivery catheter which expands to place the stent in the newly-made passage. The stent (3.3 mm inner diameter, 5.3 mm outer diameter, 2 mm in length when expanded) is composed of stainless steel and silicone that is impregnated with paclitaxel which is intended to prevent occlusion of the passage.

The largest clinical study of airway bypass published, on emphysema subjects, who had an average of 8 Exhale Drug-Eluting Stents implanted (42). Six months after the procedure, all subjects showed a statistically significant mean 400 mL decrease in RV from baseline (p=0.04) and 0.5 point decrease (p=0.025) in modified Medical Research Council (mMRC) dyspnea score. The median residual volume to total lung capacity ratio (RV/TLC) for the subjects at baseline was 0.67. For the most hyper-inflated patients (defined as those above this median) the decrease in RV at 6 months was 870 mL (p=0.022) and mMRC also decreased by 0.5 points (p=0.035). While the 17.8% improvement in forced vital capacity (FVC) over baseline for this group was not statistically significant, it was higher than the 12% generally recognized as clinically significant. Experience in this study influenced the development of the pivotal Exhale Airway Stents for Emphysema (EASE) Trial protocol which is investigating the safety and effectiveness of airway bypass in severe homogeneous emphysema patients. In the EASE Trial 42 centers enrolled 315 subjects, randomizing two airway bypass treatments to one control case. The endpoint for effectiveness was measured at 6 months. There are two primary effectiveness outcomes, forced vital capacity (FVC) and modified Medical Research Council Dyspnea Scale (mMRC), which are combined in a responder analysis. A subject is a success (responder) if their FVC improves by at least 12% of their baseline value and their mMRC improves (is reduced) by at least one point at their 6-month follow-up visit. The EASE Trial completed enrollment in April 2009. Initial results of the trial are expected to be announced sometime in 2010.

Summary

Beyond smoking cessation and oxygen therapy, LVRS is the only treatment shown to alter the natural history of emphysema. Patients with upper lobe-predominant disease, low exercise capacity, and both FEV1 and DLCO below 20% of predicted receive the most benefit, demonstrating improvements in symptoms, physiology, and reduced mortality. Most of the studies of ELVR that have so far been published have all been uncontrolled and unblinded, and as such, are open to potential bias from enthusiastic investigators and optimistic patients. They do provide encouraging, preliminary data about the safety and efficacy of these devices. The results of a multicentre randomized trial VENT trial are first major publication. Other trials are also underway which together will hopefully provide a definite indication of the future for these new technologies. It may prove to be the case that the different options will be the appropriate therapies depending to the phenotype of emphysematic disease. Only through completion of the different finished or ongoing studies will the pulmonary community learn whether ELVR therapy is in fact a clinically useful therapeutic modality.

References


