REVIEW ARTICLE

BRONCHOSCOPIC LUNG VOLUME REDUCTION/ ENDOSCOPIC EMPHYSEMA TREATMENT

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Abstract:

Chronic Obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality worldwide. It is not only the fourth leading cause of death but also leads to premature disability and is a major consumer of medical resources. This epidemic is widespread and far too common in Pakistan as it is responsible for 71 deaths per 100,000 making it the countries' fourth leading cause of death.

The abnormal and permanent enlargement of the terminal bronchioles and destruction of the alveolar units define emphysema. This destruction leads to a loss of the normal elastic recoil, which plays a role in air trapping and hyperinflation. Lung volume reduction surgery (LVRS or reduction pneumoplasty) has been shown to be a successful surgical treatment in selected patients with severe emphysema with demonstrated failure to standard medical therapy. However, surgical morbidity is high and non-pulmonary co-morbidities may preclude surgery. Given the potential for complications with LVRS and a limited pool of patients without limiting co-morbidities efforts for a minimally invasive procedure with the potential for similar outcomes have been underway. One such technique is Bronchoscopic Lung Volume Reduction (BLVRS or Endoscopic Emphysema Treatment).

The rationale for this treatment lies in the theory that the use of a blocker, sealant, device or method of ablation would lead to collapse of the emphysematous portion of the lungs and the volume reduction would have similar results to surgical resection without the morbidity of surgical procedure

INTRODUCTION

Chronic Obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality worldwide. It is not only the fourth leading cause of death but also leads to premature disability and is a major consumer of medical resources. This epidemic is widespread and far too common in Pakistan as it is responsible for 71 deaths per 100,000 making it the countries' fourth leading cause of death. This places Pakistan as the 4th highest COPD death rate among the 25 most populous countries in the world.[1] Although the current numbers are troubling, indications are that these numbers may continue to climb.[2]

Emphysema is a progressive and debilitating disease. Although it is resistant to medical treatment it is preventable. Emphysema is defined by the abnormal and permanent enlargement of the terminal bronchioles and destruction of the alveolar units. This destruction leads to a loss of the normal elastic recoil which plays a role in air trapping and hyperinflation. Hyperinflation is the primary process behind the decrease in exercise

tolerance, quality of life and the impairment in respiratory mechanics responsible for the symptoms, morbidity and mortality associated with emphysema. Hyperinflation leads to a series of changes placing the respiratory muscles, primarily the diaphragm at a mechanical disadvantage[3], [4]. This compilation of findings plays a role in dyspnea, increased work of breathing, respiratory failure and ultimately increased mortality.

Lung volume reduction surgery (LVRS or reduction pneumoplasty) has been shown to be a successful surgical treatment in selected patients with severe emphysema with demonstrated failure to standard medical therapy.[5] LVRS entails reducing the lung volume by excisions of emphysematous tissue, typically 20-30% of the upper portions of each lung, though unilateral procedures are available. However, surgical morbidity is high and non-pulmonary co-morbidities may preclude surgery. Given the potential for complications with LVRS and a limited pool of patients without limiting co-morbidities efforts for a minimally invasive procedure with the potential for similar outcomes have been underway. One such technique is Bronchoscopic Lung Volume Reduction (BLVRS or Endoscopic Emphysema Treatment).

The rationale for this treatment lies in the theory that the use of a blocker, sealant, device or method of ablation would lead to collapse of the emphysematous portion of the lungs and the volume reduction would have similar results to surgical resection without the morbidity of surgical procedure. The idea of recreating LVRS bronchoscopically is appealing. This is an approach void of an incision, possibly without general anesthesia that may treat patients deemed not suitable for surgery. Another potential benefit is that many of these techniques are reversible, which may improve the safety profile further. Bronchoscopic Lung Volume Reduction (BLVR) refers to procedures developed to treat hyperinflation due to emphysema in a minimally invasive manner via a bronchoscope. In this review we will discuss the devices and techniques employed. Several bronchoscopic interventions are currently available or are under investigation. The methods may be broken into several categories:

- Endobronchial blockade
- Tissue remodeling
- Airway bypass tracts
- Mechanical Alteration of the lung parenchyma

Endobronchial Blocking Devices and Endobronchial Valves

Endobronchial blockade was one the first techniques employed. The current endobronchial blocking device is in the form of a one-way valve. These valve systems are an evolution from the original “plugs” initially studied by Watanabe and colleagues[6] and Sabanathan and colleagues[7] in which a device was used to mechanically “block” an airway. Heterogeneous emphysema appears to be an ideal situation for such a mechanism, particularly in those patients with a significant discrepancy in the degree of emphysema between lobes or a high heterogeneity index (HI). The higher the HI the more emphysema in one lobe(s) compared to another. The intent is to prevent air from entering the targeted segment or lobe during inspiration and allow mucus and air to exit upon exhalation or cough. This will cause collapse and subsequent volume reduction through deflation and adsorption, mimicking LVRS. There were several types of devices initially studied, including: contrast filled vascular balloons, spigots and metal stents with occlusive sponges. Unfortunately, success was limited by migration, post-obstructive pneumonias and the requirement for multiple bronchoscopies.

As mentioned, the Endobronchial valves (EBV) or Intrabronchial valves (IBV) are evolved from the original blocking devices. Currently there are 2 modifications, a duck-

billed EBV and an umbrella shaped IBV. These endobronchial valves are deployed in a segmental or sub-segmental airway in a variety of manners.

The EBV is modified from an original design (Emphasys Medical, now Pulmonx, Redwood City, California, USA and Neuchatel, Switzerland) composed of a nitinol skeleton covered in silicone utilizing a duck-billed valve on the proximal end. (**Figure I**) The properties of the nitinol frame allows for movement associated with normal respiration (including coughing) while still forming a seal to prevent air entry. The EBV was originally deployed over a guide-wire. In the original procedure a guidewire was placed in the target segment, the bronchoscope was removed leaving the wire in place and the delivery catheter was then passed over the wire. Under either direct visualization or fluoroscopic guidance the valve was deployed. The most recent design of the EBV, the Zephyr® is deployed via a catheter which also acts as a sizing gauge but retains the duck-billed proximal end. This allows for deployment through the working channel of a flexible bronchoscope, though rigid deployment is also possible. There have been several case series and a multicenter analysis which showed improvement in lung function and symptoms prior to the publication of the randomized Endobronchial Valve for Emphysema Palliation Trial (VENT).[8], [9], [10]

Wan and colleagues did a retrospective analysis from a prospective multicenter registry and reported the first 98 patients with unilateral lobar placement of EBV. These patients were typical for most emphysema trials with a Forced Expiratory Volume (FEV1) between 20-40% predicted and a residual volume (RV) of approximately 244% predicted. Modest but statistically significant improvements were found in FEV1, forced expiratory volume (FVC), RV and 6 minute walk distance (6MWD), with the greatest changes noted in the patients with the lowest FEV1 and highest RV. Positive trends were also noted in patients receiving unilateral treatment and in those who achieved lobar exclusion (as opposed to 1 or 2 segments). DLCO showed no statistically significant change. Serious complications were noted in 8.2 % (8) patients and one died in the 90 day follow-up. The most common complications were pneumothoraces (3 requiring surgical intervention and four lasting greater than 7 days) and 5 pneumonias, though none were post-obstructive.[11]

The VENT study was designed to evaluate unilateral treatment of patients with severe heterogeneous emphysema (FEV1 of 15-45%) with EBV. In all, 321 patients were randomly assigned in a 2:1 fashion to have the Zephyr® EBV (220 patients) or to undergo standard medical care (101 patients).[12] The inclusion and exclusion criteria were similar to that of the National Emphysema Treatment Trial (NETT).[13] All underwent pulmonary rehabilitation with optimization of medical treatment prior to randomization. The EBV were placed under general anesthesia or moderate sedation. The results of this study showed a statistically significant improvement in FEV1, 6 MWD and the St. George's Respiratory Questionnaire (SGRQ) for the patients receiving EBV therapy compared to controls. The VENT data showed a modest improvement in spirometry and quality of life (SGRQ at 6months). FEV1 increased by 4.3% with a drop in the control leading to an improvement of 6.8% in the EBV arm. The 6 MWD showed a similar trend with an increase of 5.8% in the EBV group.

Complications were more common in the treated group as one might expect, with 6.1% of the EBV patients vs. 1.2% of the controls developing complications at 6 months. It should be noted that this met the prespecified safety criteria. Among the adverse events at 6 months were 6 deaths in EBV vs. none in the control (respiratory failure-not EBV associated (3), cancer, ischemic colitis, and massive hemoptysis). At 12 months the overall complication rate was 10.3% in EBV and 4.6% in controls. Rates of death from any cause were similar in both groups (3.7% vs. 3.5%) by 12 months. Pneumonia distal

to the valves was the most common complication occurring in 9 patients. Every instance resolved with antibiotics with 6 recovering without valve removal and 3 requiring removal. Valves were removed successfully in 85 of 87 attempts in 31 patients (range, 1 to 377 days S/P insertion). Valves were removed based on investigator judgment, not according to set protocol. Migration, distal pneumonia, COPD exacerbation, incorrect placement, hemoptysis and unspecified reasons were listed as causes.

The successful placement of the EBV may be an important factor in the overall evaluation as more than 40% of the trial sites reported technical errors of valve placement of more than 10%. This incorrect placement may have had significant impact on the final results.[14]

Subgroup analysis was performed and showed improvement for the primary endpoints (FEV1 and 6 MWD) in patients with a high Heterogeneity Index (HI) and a complete fissure. Lobar occlusion, by most accounts a primary tenant in the success of this procedure was not achieved in 43.9% of patients, and subgroup analysis showed only 39% of patients had complete fissures.[15] Identification of collateral flow may be assessed using a novel device known as The Chartis System. This is a unique tool that provides flow and pressure readings at the lobar or segmental level. This information may allow the physician to make assessments regarding the level of collateral ventilation, or inter-lobar airflow in the lungs. Collateral ventilation (CV) may limit the effectiveness of endobronchial lung-volume reduction therapy making it a potentially important predictor of EBV treatment success. Based on the subgroup analysis data from VENT it is proposed that technically proper, lobar exclusion in a patient with complete fissures may be the ideal candidate for EBV.[16]

There was also a European arm of the VENT study (EURO-VENT), in which patients were enrolled and treated using the same investigative protocol as that of the U.S. VENT study. The EURO VENT data is currently awaiting publication but was presented at The European Respiratory Society Congress in 2010 as well as The American Thoracic Society Meeting in 2011. The European responder data was consistent with the findings of the U.S. responders. Data presented suggested EBV therapy significantly improves lung function, exercise capacity and quality of life, with improved outcomes when higher lung volume reduction is achieved.[17, 18] The Zephyr® EBV has achieved CE approval in Europe (Conformite Europeenne: certifies that a product has met EU health, safety, and environmental requirements).

The second valve currently in use is termed an Intrabronchial Valve or IBV™ (Spiration Inc., Redmond, WA, USA). The IBV™ Valve System has US Food and Drug Administration (FDA) humanitarian device approval for use with selected prolonged postoperative air leaks and has received market clearance in Europe through CE mark for the treatment of diseased and damaged lung.[19]

The IBV™ is composed of a nitinol frame with 6 struts covered by a polyurethane membrane in an umbrella shape with a central rod, used for removal or repositioning. (**Figure II**) There are 5 distal anchors that set into the mucosa and limit migration. The "umbrella" will limit, redirect or inhibit flow past the IBV® while the nitinol frame will allow for mucus and air to be coughed proximally. Several valve sizes were initially used from 4-9mm in size, currently 5, 6 and 7 mm IBV are available. The process of IBV™ placement is slightly different from the Zephyr® but similarities are noted. First a balloon is carefully calibrated to several standardized diameters allowing it to serve as a measuring device. This balloon is then inflated in each segment to be treated and the correct IBV™ size is chosen. The IBV™ are loaded into a catheter and deployed through the working channel of a flexible bronchoscope under direct visualization.

The initial pilot study was a multicenter, prospective, open-enrollment cohort study which included 30 patients in 5 centers. Patients were similar in the enrollment criteria for

NETT. There were no statistically significant improvements in physiologic testing but patients demonstrated improvements in health related quality of life (HRQL) with a 6.8 unit change in the SGRQ. The conclusion by the authors was the IBV is a safe, feasible, easy to learn and perform procedure with an acceptable safety profile. The authors added a bilateral upper lobe procedure with quality of life measures and regional volume shifts may be the best targets.[20]

A phase II multicenter pilot study involving 91 patients has been performed assessing safety as its primary endpoint. The patients evaluated had severe obstruction, hyperinflation and upper lobe predominant emphysema. A median of 6.0 IBV™ were placed in each subject with a 99.7% technical success rate. No migration or erosion was seen. This study did meet its primary endpoint of safety based on no valve migration or erosion and a 2.5% rate of associated infection. The mean SGRQ change exceeds a clinically meaningful 4-point change. [21], [22] This was seen at all time points and was statistically significant. No reported procedure related deaths, 30-day morbidity and mortality was 5.5% and 1.1%, respectively. Forty-four valves were removed in 16 patients for concerns of bronchospasm, pneumonia, recurrent COPD exacerbations and pneumothorax. At 6 months significant improvements in HRQL measured by the SGRQ (-8.2 +/- 16.2, p=0.001) were seen. These improvements correlated with a decrease in lung volumes (-294 +/- 427, p=0.007) in treated lobes with visible atelectasis. There was no significant change in FEV1, 6 MWD or exercise ergometry.[23]

While there was no significant change in FEV1, one can argue that HRQL as measured by the SGRQ may be more clinically relevant if our primary goal is to improve patient's symptoms (and possibly mortality) rather than a physiologic parameter. As an example, pulmonary rehabilitation does not impact FEV1 but has been shown to significantly improve dyspnea, exercise capacity and HRQL.[24] Additional evidence suggests dyspnea may be a better predictor of survival than FEV1 in severe COPD and so authors argue that SGRQ may be a more optimal endpoint in this population.[25]

Quantitative CT analysis of lung volumes showed a decrease in volumes (335 +/- 444ml) in 88% of the cohort, though only 57 subjects had this analysis. The untreated lobes showed a concomitant increase in volume of 11.6%. The volume changes were associated with clinically meaningful improvements in SGRQ but not with objective pulmonary function testing.[26]

A multicenter randomized, double-blinded, placebo controlled study has closed to enrollment and results are anticipated to be released in 2012.

One proposed mechanism for the modest improvement in patients following IBV or EBV treatment might be collateral ventilation. The original hypothesis of BLVRS was that an endobronchial blocking device would lead to cessation of air flow and subsequent lobar atelectasis. This lobar exclusion could then recreate the effects of surgical excision of the high HI diseased lung. Incomplete lobar fissures are a primary source for collateral ventilation and hence limit resorption atelectasis. The ability to identify patients with absence of collateral ventilation may lead to a better outcome. There is much debate on the best approach for BLVRS. Should one attempt to achieve complete lobar atelectasis or is a sub-lobar treatment, possibly with less risk of pneumothoraces more favorable? As mentioned in the VENT trial, it appeared that the subgroups with less collateral flow i.e. complete fissures and complete lobar occlusion may be the best targets. Hopkinson and colleagues looked at that aspect and concluded that lobar atelectasis was indeed associated with an improved survival. In their group 100% of those that achieved atelectasis were alive at 6 years compared to only 43% of those who did not develop atelectasis.[27] This group was treated in a unilateral fashion as opposed to the IBV group. Additionally, the IBV group was treated for incomplete lobar exclusion, though in the subgroup in which atelectasis did develop (9 patients, 9%) it was associated with

significant improvements in lung volumes as well as a greater improvement in the SGRQ.[28]

Tissue Remodeling

There are two distinct pathways being pursued, thermal ablation and biologic/chemical ablation, which share ultimate goal of achieving volume reduction. Simply, these strategies strive to pertinently alter the lung parenchyma by inducing inflammatory changes and scarring. These approaches differ from many of the mechanical techniques since they are not constrained by collateral ventilation and no foreign body is placed in the lung.

It is hypothesized that thermal ablation of emphysematous lung can be achieve by applying specific doses of steam to a segmental bronchus. This is thought to produce an inflammatory response that results in lung volume reduction. A nonreusable 2 mm vapor catheter is inserted via flexible bronchoscopy to the target airways. There is a balloon at the distal end of the catheter to localize the application of steam to a specific segment. A precise dose of steam generated by an electronically controlled pressure vessel is then delivered to the isolated airways.[29]

In a safety and feasibility trial, 11 patients with heterogeneous emphysema were treated unilaterally with a dose of 5 calories per gram of lung tissue. Lung tissue weight was estimated from CT volume and density analysis. There were no recorded improvements in spirometry but mean St. George's Respiratory Questionnaire scores dropped 15.3 units from 64.4 to 49.1 over 6 months. Adverse events included COPD exacerbations in 4 patients and 2 episodes of pneumonitis.[29] This technology remains an investigational and trials are underway to further assess safety and efficacy long term

Another approach to BLVRS is Biologic lung volume reduction (BioLVR). BioLVR aims to induce lung volume reduction through tissue remodeling. BioLVR involves instilling a sealant or remodeling agent, which initiates an inflammatory reaction, scarring and resultant segmental or lobar collapse thus causing volume reduction. The original technique used a fibrin-thrombin mixture and although moderately successful a revised reagent was developed using a hydrogel (**Figure III**). The hydrogel contains biodegradable Chondroitin sulfate and poly-L-lysine that cause an inflammatory reaction leading to collapse, remodeling and volume reduction over several weeks.[30]

Once the target segment is identified the bronchoscope is introduced and wedged into the airway. Suction is applied in an attempt to induce distal collapse. A primer solution containing porcine trypsin is then instilled through the working channel of the bronchoscope. This is intended to promote detachment of epithelial cells and deactivate surfactant.[29] The primer is suctioned after 2 minutes and 10mL of cell culture media is instilled in order to wash out the primer. A dual lumen catheter is then inserted into the target segment/sub-segment. The fibrinogen and thrombin are injected simultaneously and mix distal to the catheter. This is followed by 60mL of air to push these reagents distally. The components mix and polymerize into a hydrogel.[31]

The Aeris Polymeric Lung Volume Reduction (PLVR) System (Aeris Therapeutics, Inc. Woburn, MA, USA) is another novel therapeutic system being developed and evaluated for both heterogeneous and homogeneous emphysema. PLVR exerts its effects using a Hydrogel-Foam that is instilled into emphysematous segments. The material will polymerize and adhere to tissue, as the gas within the polymer is absorbed it leads to collapse. This collapse will result in improved recoil and volume reduction and, ideally a therapeutic benefit. We will summarize several selected studies.

The original technique has been used in sheep models of papain induced emphysema demonstrating reproducible volume reduction. [30] BioLVR demonstrated a 16% reduction in total lung capacity and a 55% reduction in RV with no evidence of infection. Scar formation was demonstrated in 91% of the treated segments.[31]

An open labeled phase I trial by Reilly and colleagues was performed to evaluate the safety of BioLVR in patients with UL predominant emphysema with a 3 month follow-up. Three patients received unilateral treatment at 2 subsegments and 3 received unilateral treatment at 4 subsegments. Adverse events (AE) and changes in pulmonary function were evaluated. All patients were discharged on post-procedure day 1. Safety was the primary endpoint and no serious AE were observed. Improvements were noted in mean vital capacity (+7.2 +/- 9.5%; range, -2% to +19%), mean residual volume (RV) [-7.8 +/- 8.5%; range, -1% to + 22%], mean RV/total lung capacity ratio (-6.6 +/- 4.7%; range, -1% to -15%), mean 6MWD (+14.5 +/- 18.5%; range, 0 to + 51%), and in mean dyspnea score. On average, the patients who received treatment in 4 subsegments experienced a greater benefit from BioLVR, suggesting a dose-response pattern.[32] (**Figure IV**)

In a phase II study 22 patients with UL predominant emphysema were treated with 20 mL of hydrogel per subsegment and 28 with 10mL per subsegment. [33] At the 6 month follow-up there was an improvement in FVC, FEV1 and RV that was greater in the high dose group compared to the low dose group. Chest CT showed scarring and atelectasis in the high dose group. Compared to baseline there was no change in the 6MWD. In 25 patients with bilateral homogeneous emphysema similar findings were reported.[34]

Later a synthetic polymeric foam sealant known as emphysematous lung sealant (ELS, AeriSeal®) was evaluated in 25 patients with heterogeneous emphysema. The number of subsegment sites treated at one time varied from two to four. Modest improvements in air trapping and gas transfer were seen in patients with GOLD stage III, but not in those with GOLD stage IV. Two of five patients noted a clinical benefit after a second instillation, again pointing towards a dose dependent effect.[35]

Flu-like symptoms including fever, pleuritic chest pain, dyspnea, nausea, headache, malaise and leukocytosis were noted in over 90% but quickly resolved.[34]

BioLVRS appears to be a safe, well tolerated procedure that may be dose dependent. If the amount of lung tissues equivalent to LVRS is to be treated then instillation of up to 12 segments may be required. [36] One potential advantage to this technique is interalveolar as well as bronchiolar-alveolar communications are sealed which will negate any collateral flow. As previously mentioned, collateral flow has been implicated as a possible source of failure or limited success with other techniques. However, in contrast to EBV or IBV, once the reagent is administered the effects are thought to be irreversible though it is unclear if some degradation may occur over time. Further evaluation is warranted and underway.

Airway Bypass

Airway bypass is a bronchoscopic lung-volume reduction procedure for emphysema whereby transbronchial passages into the lung are created, between emphysematous lung and distal bronchi, to release trapped air, supported with paclitaxel-coated stents to ease the mechanics of breathing.[37] This approach is dependent on what could be argued is the Achilles heel of the valve trials, collateral ventilation. While collateral ventilation generally is not a factor in structurally “normal” lungs, in patients with emphysema where airway resistance is high there significant flow through these paths can be seen.[38] The technique targeted patients with homogeneous emphysema in whom airway resistance is high and the presence of collateral ventilation thought to be greatest. The bypass tracts were to become new low resistance bronchial fenestrations to allow trapped air to escape by circumventing high resistance airways. The more distal

emphysematous segments would communicate with the bypass tracts via collateral ventilation. The result would be in diminished hyperinflation and improved lung compliance in part by reductions in dead space. It should be noted that this improvement in lung compliance occurs without actual change in the elastic properties of the lung.[39]

In the EASE trial the airway bypass procedures was performed on patients with homogenous emphysema and considerable hyperinflation. There are 3 steps that are performed via flexible bronchoscopy: confirmation of an area of the segmental bronchi that is free from blood vessels using a Doppler probe, fenestration of the airways, and placement of a paclitaxel eluting stent. Paclitaxel is a mitotic inhibitor that prevents granulation tissue from obstructing the stent.[37]

The results of the EASE trial, a randomized, double blind, sham-controlled study were recently published. 315 patients with severe hyperinflation (ratio of residual volume [RV] to total lung capacity of ≥0·65) were randomized in a 2:1 distribution. For patient's randomized to the treatment arm fenestrations were created and up to six stents (maximum of two stents per lobe, excluding the right middle lobe). Participants were followed for 12 months. The 6-month co-primary efficacy endpoint required 12% or greater improvement in forced vital capacity (FVC) and 1 point or greater decrease in the modified Medical Research Council dyspnea score from baseline. The composite primary safety endpoint incorporated five severe adverse events. At 6 months, no difference between treatment arms was noted with respect to the co-primary efficacy endpoint (30 of 208 for airway bypass vs. 12 of 107 for sham control; posterior probability 0·749, below the Bayesian success threshold of 0·965). The 6-month composite primary safety endpoint was 14·4% (30 of 208) for airway bypass versus 11·2% (12 of 107) for sham control (judged non-inferior, with a posterior probability of 1·00 [Bayesian success threshold >0·95]). While the findings showed safety and transient improvements, no sustainable benefit was recorded with airway bypass in patients with severe homogeneous emphysema.[40]

In an earlier study one death from hemoptysis was reported with airway bypass procedures. Data and safety monitoring board review of the fatal hemoptysis had the following recommendations which were incorporated into the EASE trial: placement of an endobronchial balloon blocker in the main bronchus as well as Doppler rescanning between fenestration creation and stent deployment. Post-procedure complications occurred in 59% of cases with; COPD exacerbation in 32%, pneumomediastinum in 5% and respiratory infection in 27%. At follow-up bronchoscopy 6 months later, 69% of stents remained patent.[41] Granulation tissue, radial traction by the surrounding airways and secretions are as possible causes of stent occlusion[42].

Mechanical Alteration of the lung parenchyma

Airway implants such as nitinol coils of 10 to 20 cm in length have been designed for use in patients with either homogeneous or heterogeneous emphysema (**Figure V**). The nitinol coils are easily straightened within the delivery catheter only to return to its entropic position within the lung. The lung then tethers around the coil. The coils are inserted under fluoroscopic visualization with each insertion taking less than 2 minutes (**Figure VI**). Preliminary safety data on 11 patients have shown no evidence of pneumothorax or severe adverse events. Maximal reduction in lung volume occurred between 2 to 4 weeks after implantation and there is some suggestion of improvements in spirometry, exercise capacity, and quality of life. The trend was for greater improvement in patients with heterogeneous emphysema[43]. This technology remains an investigational and trials are underway to further assess safety and efficacy long term

Conclusion

BLVRS is an exciting field under investigation in Thoracic Medicine as evidence by the numerous trials and competing devices. The ultimate goal is to provide changes consistent with or superior to LVRS with less morbidity and mortality at a cost which will allow the technology to disseminate the world over. No answers are clear at present due to limited numbers of patients studied and short length of follow-up. As our experience in varied endobronchial modalities grows, as well as our understanding of how emphysema responds to such we may better define an ideal group for BLVRS. Patients with a high HI, complete lobar fissures, in which a complete lobar approach yields atelectasis, may be our target population. Presently we do not know if a unilateral or bilateral approach will be more beneficial. If our goal is to compete for changes comparable to LVRS then a trial against the gold standard may be in order. However, it may be that this is a viable option for those too ill to undergo LVRS or as a bridge to LVRS or transplant. Many questions remain unanswered, but as long as we continue to expand our experience in a scientific manner it will only be a matter of time.

Table I summarizes Multicenter Trials

Study	Patients	Unilateral or Bilateral Treatment	Lobar Exclusion	Outcomes (6 months unless noted)	% Complication rates
Wan et[44]	98	U 64 B 34	U/L 48 B/L 21	At 3 mo FEV1: _10.7 _ 26.2% 6 MW: _23 _ 55.3 m	At 3 mo Death: 1 (1/98) Pneumothorax: 3 (3/98) BPF: 4 (4/98) AECOPD: 17 (17/98)
Sciurba et el (VENT Study)[45]	220 101	U	All targeted	SGRQ: _2.8 (_4.7 to _1.0) FEV1: _4.3% (1.4 to 7.2) Median 6 MW: _2.5% (_1.1 to 6.1) Lobar exclusion: 109/194 (56.2%)	3 mo Composite complication rate: 4.2% (9/214) PTX: 4.2 (9/214) AECOPD: 9.3 (20/214) Pneumonia: 3.2 (7/214) Hemoptysis: 5.6 (12/214) 85 valves removed from 31 patients (12 mo)
Herth et al (EURO VENT Study) [46]	111 60	U	All targeted	SGRQ: _4.8 (_46.3 to 22.8) FEV1: _6.6% (_32.3 to	6 mo Composite complication rate: 13.5% (15/111), including PTX: 4.5 (5/111)

				70.0) 6 MW: _8.8% (_50.0 to 161.7)	Pneumonia: 4.5 (5/111) Hemoptysis: 0.9 (1/111) Respiratory failure: 3.6 (4/111)
Sterman et al [47]	91	B 88 U 3	Mix of lobar and non-lobar exclusion due to protocol change during study	SGRQ -8.2 +/- 16.2 > or = 4 points: 55.7% Atelectasis: 9.2% No sig change : FEV1 and 6MWD	12 months Deaths: 2 (2/91) tension PTX PTX: 11 (11/91) AECOPD: 7 (7/91) 1 respiratory distress & myocardial infarction 44 Valves removed in 16 patients

AECOPD, acute exacerbation of COPD; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; 6 MW, 6-minute walk. ATX, Atelectasis

Figure I Zephyr® EBV (Emphasys Medical, now Pulmonx, Redwood City, California, USA and Neuchatel, Switzerland)

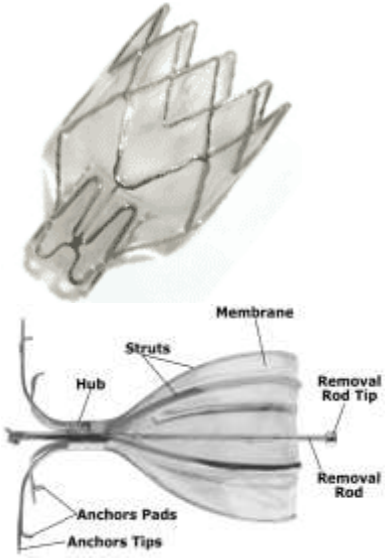

Figure II
IBV™, Spiration Inc. (Redmond, WA, USA)

Figure III BioLVR system

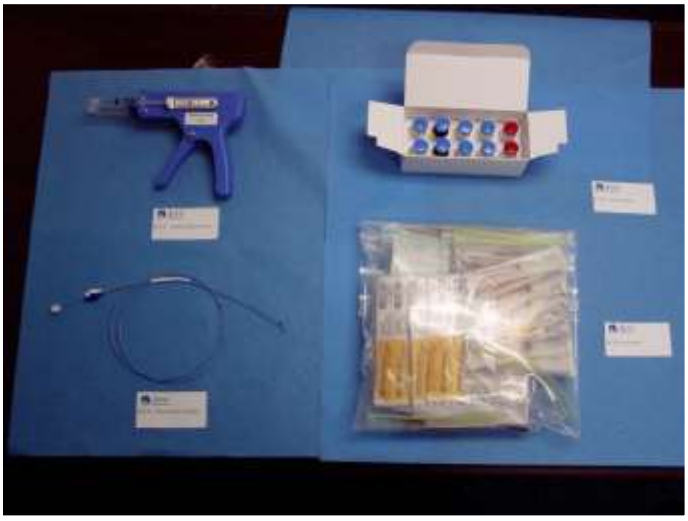

Figure IV
CT scans below demonstrate increased atelectasis and scarring associated with increasing dose.[48]

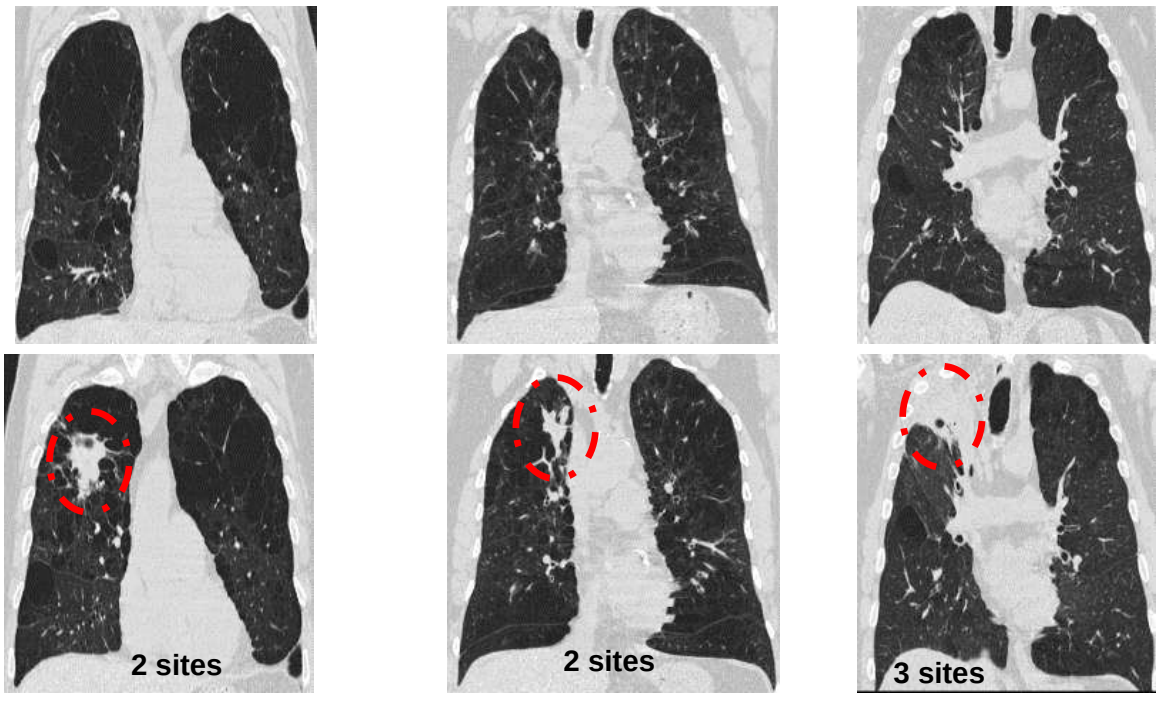

Image 6

Figure 4. Thoracic X-ray (Posterior-Anterior view) showing the Lung Volume Reduction coils in situ in all segments of both upper lobes.

[1] Herth FJ, Gompelmann D, Stanzel F, Bonnet R, Behr J, Schmidt B, Magnussen H, Ernst A, Eberhardt R Treatment of advanced emphysema with emphysematous lung sealant (AeriSeal®). Respiration. 2011;82(1):36.

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Figure V

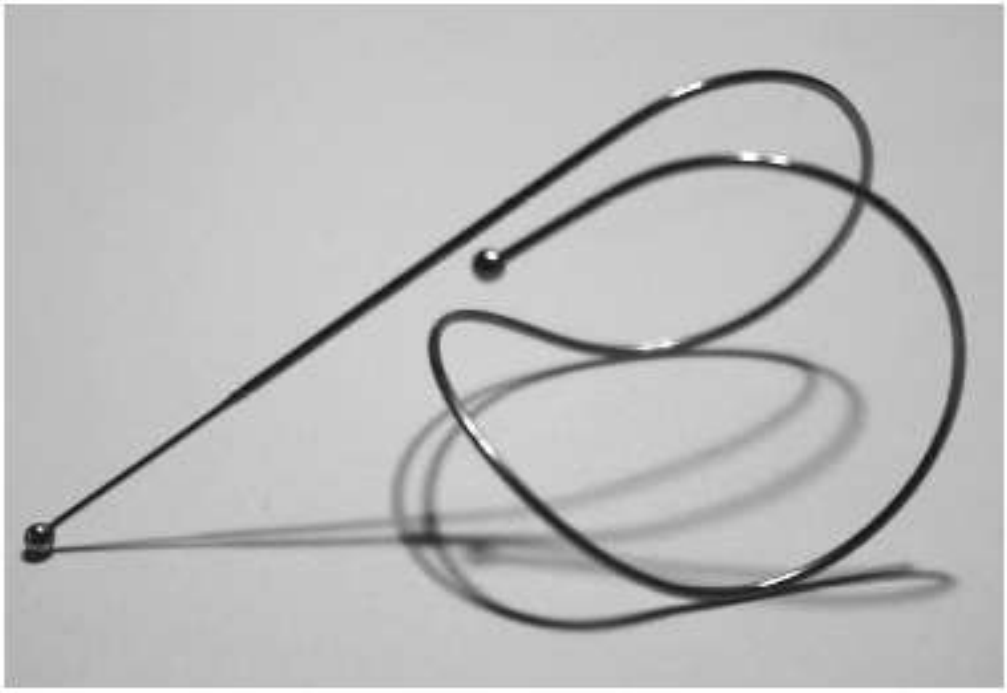

figure 1, RePneu® Lung Volume Reduction Coil (150mm size).
185x126mm (150 x 150 DPI)

Figure VI

Figure 4. Thoracic X-ray (Posterior-Anterior view) showing the Lung Volume Reduction coils in situ in all segments of both upper lobes.