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Lung Volume Reduction as an Alternative to Transplantation for COPD

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Abstract

Emphysema is disabling and progressive and hallmarked by decreased exercise tolerance and impaired quality of life. Hyperinflation is the sentinel physiological characteristic of emphysema that is responsible for exercise intolerance, dyspnea, impaired quality of life and high mortality. Medical treatment does not alter the progression of emphysema and has little effect on palliating dyspnea or improving functional performance or quality of life. Surgical interventions that reduce lung volume have been the focus of multiple interventions for decades; however, until recently, limited evidence has documented their effectiveness. Lung volume reduction surgery (LVRS) underwent rigorous study in the National Emphysema Treatment Trial (NETT), which demonstrated its short and long term effectiveness, associated morbidity and mortality and the essential factors that predict LVRS success or failure. Current investigation focuses on the use of less invasive techniques, predominantly bronchoscopic techniques that reduce lung volume without open thoracotomy. Herein, I summarize the major results of the NETT and briefly review newer bronchoscopic lung volume reduction techniques that show promise as alternative treatments for select COPD patients undergoing consideration for lung transplantation.

Introduction

Emphysema is a progressive and debilitating disease that is recalcitrant to medical interventions. Hyperinflation is the sentinel complication of emphysema that decreases exercise performance and quality of life, impairs respiratory muscle and chest wall mechanics, increases breathlessness, prolongs respiratory failure requiring mechanical ventilation and increases mortality (1–4). Recent evidence suggests that hyperinflation has implications that go far beyond the respiratory system and may also exert its negative effects on exercise performance and mortality by reducing cardiac chamber size and impairing right and left ventricular function. (5–7) It may also heighten systemic inflammation. (8).

Lung volume reduction surgery (LVRS) was devised with the intent of mitigating the degree and impact of hyperinflation. Prior to the National Emphysema Treatment Trial (NETT), data regarding LVRS consisted mainly of uncontrolled, single center studies that were characterized by small patient numbers, substantial variability in patient selection criteria

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and surgical approach, duration of follow-up and definitions of complications and outcomes. (9–17) NETT was a randomized, controlled, prospective, multicenter, long-term trial designed to provide definitive answers regarding the independent effects of LVRS in comparison to medical therapy on survival as well as exercise performance, lung function, patient symptoms and quality of life. (18) NETT demonstrated a 5.2% ninety-day post-operative mortality compared to 1.5% with optimal medical therapy. This risk is acceptable to many severely impaired emphysema patients, but other patients remain apprehensive and forego LVRS and await less invasive therapeutic options. (19, 20) In May 2003 soon after the publication of NETT results, interest grew in non-surgical bronchoscopic approaches to lung volume reduction (BLVR). (21–29)

Herein I review the effects of LVRS in comparison to medical therapy, characterize the optimum candidate for LVRS and provide an up-to-date review of the various experimental bronchoscopic lung reduction techniques that are currently undergoing investigation.

Lung Volume Reduction Surgery (LVRS)

In 2003, the results of the NETT were published, detailing the effects of LVRS on survival and maximum exercise capacity in 1,218 emphysema patients who were randomized to LVRS or medical treatment between January 1998 and July 2002 and followed for a mean of 2.4 years. (30) NETT also reported the effects of LVRS on pulmonary function, oxygen requirement, 6 minute walk distance (6MWD), quality of life, respiratory symptoms, and health care utilization. In 2006, the NETT Research Group published updated analyses of survival and functional measures data with a median follow-up of 4.3 years. (31) These analyses included 40% more patients with functional measures at 2 years after randomization compared to the original 2003 outcomes report. Subsequent NETT publications reported on the prevalence and duration of air leaks, (32), optimum surgical approach to perform LVRS (33) and cost effectiveness of the procedure. (34, 35) The major findings of these reports are summarized below.

Major Outcomes in NETT: All Patients

Between January 1998 and July 2002, 3777 patients were screened for NETT and 1218 underwent randomization: 608 to LVRS and 610 to medical treatment. Baseline characteristics (Table 1) were similar between groups. Of 608 patients assigned to LVRS, 580 (95.4%) underwent LVRS [(406 (70%) by median sternotomy, 174 (30%) by video-assisted thoracoscopic surgery], 21 (3.5%) declined LVRS and 7 (1.2%) were considered unsuitable by the surgeon for LVRS.

Ninety-day mortality rate was 7.9% (95% confidence interval, 5.9–10.3%) in the LVRS group compared to 1.3% in the medical group (95% confidence interval, 0.6–2.6%, $p < 0.001$). At a mean follow-up of 29.2 months post randomization, 160 patients assigned to medical treatment died compared to 157 patients assigned to LVRS. There was no difference in mortality rates at this time point between groups although a higher initial mortality rate was identified in the LVRS group soon after the operation (Figure 1a).

Exercise capacity improved ≥ 10 W in 28%, 22% and 15 % of LVRS patients after 6, 12 and 24 months, respectively compared to 4%, 5% and 3% of medical control patients ($p < 0.001$ at each time point, Table 2 and Figure 2). Additionally, patients who underwent LVRS were more likely to demonstrate improvements in 6MWD, % predicted forced expiratory volume in one-second (FEV_1), severity of dyspnea, and general- as well as disease-specific quality of life assessments compared to the control group (Table 2 and Figure 2).

Identifying a Patient Subgroup at High Risk of Death Following LVRS

Before NETT commenced, a 30-day surgical mortality greater than 8% in either treatment group was defined as a stopping endpoint. In May 2001, a subgroup defined by $FEV_1 \leq 20\%$ predicted and either a diffusing capacity for carbon monoxide ($DL_{CO} \leq 20\%$ predicted or homogeneous emphysema met the pre-specified stopping criteria because of excessive mortality with LVRS. (36) The 30-day mortality in those who received LVRS was 16% (95% confidence interval, 8.2–26.7%, $p < 0.001$) compared to no deaths in the medical group. For those “high risk profile” LVRS-treated patients who survived 6-months post randomization, there was little or no difference in functional and quality of life outcomes compared to the medically treated group: exercise capacity increased by 4.5 ± 13.0 watts (W) vs. a decrease of 4.4 ± 14.8 W, $p=0.06$), 6 MWD increased by 14.9 ± 63.7 meters (m) vs. a decrease of 21.6 ± 56.7 m, $p=0.03$), and FEV_1 increased by $5.5 \pm 6.9\%$ predicted vs. a decrease of $0.4 \pm 1.9\%$ predicted, $p < 0.001$). At six months, the Quality of Well-Being score showed a similar decrease (0.01 units) for both groups.

As described by the above data, severe emphysema patients characterized by an $FEV_1 \leq 20\%$ predicted and either a homogeneous pattern of emphysema on chest CT or a $DL_{CO} \leq 20\%$ predicted have high postoperative LVRS mortality and little chance of clinically meaningful improvements in lung function, exercise tolerance or quality of life. As a result, these types of patients are not approved for LVRS by the Centers for Medicare and Medicaid Services (CMS) or by the Joint Commission for the Accreditation of Healthcare Organization (JCAHO) guidelines.

Results of NETT: Outcomes in Non-High Risk Patients

Among 1,078 NETT patients who were not high risk, the 30-day mortality after LVRS was 2.2% and 0.2% after medical treatment ($p < 0.001$). Ninety-day mortality rate was 5.2% with LVRS and 1.5% with medical therapy ($p=0.001$; Table 3). At a mean 29.2 months follow-up after randomization into NETT, LVRS provided no survival benefit over medical treatment, even with exclusion of the high risk for death subgroup. Patients who underwent LVRS more likely had improvements in 6MWD, maximum exercise capacity, $FEV_1\%$ predicted and quality of life (disease specific and general) compared with continued medical treatment ($P < 0.001$ for each comparison; Figure 2).

Pre-operative Predictors of LVRS Outcomes in Non-High Risk NETT Patients

The baseline factors associated with differences in mortality, functional outcomes, and quality of life outcomes between the treatment groups were the craniocaudal distribution of emphysema on chest CT (presence or absence of upper lobe predominant emphysema, p for interaction= 0.02) and post rehabilitation exercise test maximum wattage (low or high exercise, p for interaction=0.01).

Based on combinations of high and low exercise maximum wattage with upper lobe or non-upper lobe predominant emphysema by chest CT analyses, patients were divided into 4 subgroups. In the 290 patients with upper lobe predominant emphysema and low exercise capacity, LVRS had a lower risk of death than medical therapy (RR 0.47, $p=0.005$, Figure 1D and Table 3). This LVRS subgroup more likely achieved ≥ 10 W improvement in maximum exercise wattage at 24 months (30% vs. 0%; $p < 0.001$, Table 2) and $\geq$ an 8 point improvement in St. George's Respiratory Questionnaire (SGRQ) score at 24 months (48% vs. 10%, $p < 0.001$, Table 2). In 419 patients with upper lobe predominant emphysema and high exercise wattage, LVRS had no impact on survival (RR 0.98; $p=0.70$). However, LVRS patients were more likely to have ≥ 10 W improvement in maximum exercise wattage at 24 months (15% vs. 3%, $p=0.001$, Table 2) and $\geq$ an 8 point improvement in SGRQ (41% vs. 11%, $p < 0.001$, Table 2) compared to medical therapy. In 149 patients with non-upper lobe

predominant disease and low exercise capacity, LVRS had no impact on risk of death (RR 0.81; $p=0.49$) or maximum exercise capacity at 24 months (12% vs. 7%, $p=0.50$). However, LVRS was more likely to improve SGRQ at 24 months (37% vs. 7%, $p=0.001$, Table 2). In 220 patients with non-upper lobe predominant emphysema and high exercise at baseline, LVRS increased the risk for death (RR 2.06, $p=0.02$) and had no effect on maximum exercise capacity at 24 months (3% both groups, $p=1.0$) or SGRQ (15% vs. 12%, $p=0.61$; Table 2).

NETT: Long-term Follow-up

At the time of the initial NETT publication, mean follow-up was only 2.4 years. An assessment of follow-up at a later time point was proposed by the NETT Steering Committee to establish the durability of benefits from LVRS on functional and physiological performance, and also to assess the effect of LVRS on long-term survival. Enrolled patients continued to have regularly scheduled follow-up tests, telephone interviews, clinic visits, and completed quality of life questionnaires. Long-term survival was updated by clinical center reports and review of the Social Security Master Death file. Figure 3A shows probability of death as a function of years post LVRS or medical treatment in all 1218 patients, with a median follow-up of 4.3 years. (31) Total mortality rate was 0.11 deaths per person-year with LVRS and 0.13 with medical therapy, respectively (RR 0.85, $p=0.02$). Survival was improved with LVRS compared to medical treatment despite the expected higher earlier postoperative mortality following LVRS.

Exercise capacity improved ≥ 10 W in 23%, 15% and 9% of LVRS patients compared with 5%, 3% and 1% of the medical patients at follow-up of 1, 2 and 3 years ($p < 0.001$ at each time point). After LVRS, SGRQ decreased > 8 units in 40%, 32%, 20% 10% and 13% compared to 9%, 8%, 8%, 4% and 7% following medical care at 1–5 years follow-up ($p<0.001$ years 1–3; $p=0.005$, year 4; $p=0.12$, year 5).

Effect of LVRS Subgroup Classification on Long-term Survival and Functional Outcome Following LVRS

The updated analyses provided additional support for assessing the differential risks and benefits of LVRS by classifying patients using the pattern of emphysema on chest CT and maximum wattage attained on post pulmonary rehabilitation exercise testing. In 290 patients with upper lobe predominant emphysema and low exercise capacity, LVRS provided a substantial survival advantage compared to medical treatment (RR 0.57, $p=0.01$, Figure 3c). Those patients who underwent LVRS also had significantly improved exercise capacity and quality of life (Figure 4c and Figure 5c, respectively).

Operative Mortality and Cardiopulmonary Morbidity following LVRS

A secondary goal of NETT was to develop predictors of LVRS mortality and morbidity. (37) A number of predictors of mortality and morbidity were analyzed in 511 non high-risk patients who underwent LVRS. These factors included: demographic characteristics, pulmonary function, the extent and pattern of emphysema on chest CT, maximum wattage attained during exercise testing, dyspnea and quality of life. Major pulmonary morbidity was defined as tracheostomy, failure to wean from mechanical ventilation, pneumonia, re-intubation, or mechanical ventilation > 3 days within 30 days of surgery. Major cardiovascular morbidity was defined as myocardial infarction, pulmonary embolus, or cardiac arrhythmia requiring treatment within 30 days of LVRS.

Within 90 days of LVRS, the incidence of operative mortality was 5.5%; major pulmonary and cardiovascular morbidity occurred in 29.8% and 20% of patients, respectively. Intra-operatively, 91% of patients had no complications, 2.2% had transient hypoxemia and 1.2%

had an arrhythmia. 58.7% of patients had at least one post-operative complication within 30 days of LVRS. Arrhythmia was the most common complication and occurred in 23.5%. Pneumonia developed in 18.2%, 21.8% required at least 1 re-intubation, 11.7% were readmitted to the ICU, 8.2% underwent tracheostomy, and 5.1% of patients failed weaning from mechanical ventilation within 3 days post LVRS.

The presence of non-upper lobe predominant emphysema was the sole predictor of operative mortality (relative odds 2.99, $p=0.009$). Pulmonary morbidity was greater in older patients (relative odds 1.05, $p=0.02$), and those with lower FEV₁ (relative odds 0.97, $p=0.05$) or DL_{CO} (relative odds 0.97, $p=0.01$). Cardiovascular morbidity was higher in older patients (relative odds 1.07, $p=0.004$), those who used oral steroids (relative odds 1.72, $p=0.04$) or with non-upper lobe predominant emphysema (relative odds 2.67, $p<0.001$).

LVRS and Air Leaks

Air leaks are common after LVRS and may be prolonged. NETT investigated the effects of a variety of buttressing products and techniques on preventing postoperative air leaks. (32) Following LVRS, 496 of the 552 patients (89.8%) had air leaks at some point within 30 days of surgery. The median duration of air leaks was 7 days, but 66 patients (11.9%) had air leaks ≥ 30 days postoperatively. Air leak duration was longer in Caucasians ($p<0.0001$) and in association with lower FEV₁ ($p=0.0003$) or diffusion capacity ($p=0.06$), use of inhaled steroids ($p=0.004$), upper lobe predominant emphysema ($p=0.04$), and presence of pleural adhesions ($p=0.007$). Surgical approach [median sternotomy (MS) vs. video-assisted thorascopic surgery (VATS)] and the use of buttressing materials and stapler brand did not influence air leak duration. Postoperative complications were greater in patients with air leaks (57% vs. 30%, $p=0.0004$) and postoperative stay was longer (11.8 ± 6.5 days vs. 7.6 ± 4.4 days, $p=0.0005$).

Surgical Approach and LVRS Outcomes

NETT also compared the effects of LVRS surgical approaches via MS or VATS on patient mortality, morbidity and functional outcomes. (33) Ninety-day mortality was similar for the two groups: 5.9% for MS and 4.6% for VATS ($p=0.67$). Overall mortality was 0.08 deaths per person-year for MS and 0.10 deaths per person-year for VATS (VATS: MS RR 1.18, $p=0.42$). There were no significant differences between MS and VATS in mean intra-operative blood loss, or transfusion needs. Mean operating time was 21.7 minutes shorter for MS than VATS ($p<0.001$), hypoxemia was less frequent with MS than VATS (0.8% vs. 5.3%, $p=0.004$), and intra-operative complications were less with MS compared to VATS (93% vs. 86.2% no intra-operative complications, $p=0.02$).

Median hospital length of stay was longer for MS than VATS but the difference was not statistically significant (10 vs. 9 days; $p=0.1$). At 30 days following LVRS, 70.5% of MS patients were living independently compared to 80.9% of VATS patients ($p=0.02$). Functional outcomes were similar between groups at 12 and 24 months of follow-up. Costs related to LVRS and associated hospitalization were less for VATS compared to MS ($p=0.03$), as were total costs (medical and non medical) during the 6 months after LVRS ($P=0.005$).

Lung Volume Reduction: Investigational Approaches

Despite the many benefits that may result from LVRS, many patients find the operative risks to be unacceptable and forego surgery. In 2004, only 254 Medicare beneficiaries underwent LVRS at 42 approved centers; in 2005 and 2006 only 120 and 105 Medicare beneficiaries underwent LVRS, respectively. Soon after the initial NETT results were published in 2003, scientific and commercial interest grew in non-surgical approaches to lung volume reduction

(LVR) in an attempt to achieve similar physiological and functional benefits to LVRS but with less morbidity and mortality. (21–29)

Investigative approaches to LVR can be broken down into five main categories: 1) one-way endobronchial valves implanted into the airway; 2) self activating coils placed into the airway; 3) targeted destruction and remodeling of emphysematous tissue; 4) bypass tract airway stenting and 5) transpleural ventilation (Table 4). One-way endobronchial valves work by promoting atelectasis by regionally blocking inspiration but permitting expiration. Self-activating coils that are placed into the airway induce atelectasis and volume reduction by assuming their preformed coil shape and bending the airway and collapsing the surrounding lung tissue. Targeted destruction and remodeling of emphysematous tissue has been accomplished by Biological Lung Volume Reduction (BioLVR), which is the regional instillation of biological adhesives that collapse and remodel emphysematous regions; and by Bronchoscopic Thermal Vapour Ablation (BTVA), which heats and destroys targeted emphysematous lung tissue. During airway bypass tract stenting, stents are placed endobronchially into emphysematous lung tissue to enhance the emptying of damaged lung tissue with prolonged expiratory time constants. The same rationale is used with transpleural ventilation techniques in which modified chest tubes are placed transthoracically into emphysematous lung tissue to empty damaged lung externally outside the chest cavity.

The above techniques all attempt to achieve sustained reductions in end-expiratory lung volume, but all differ in the approach, the effect of collateral ventilation or non-intact pleural fissures on success in achieving lung reduction and also the reversibility or irreversibility of the treatment intervention. Each of the above techniques is discussed in detail below. Table 4 compares the major features of each of the above approaches.

Endobronchial One-Way Valves

Endobronchial valve systems are deployed into segmental or sub-segmental bronchi through a flexible or rigid bronchoscope using a catheter or guide wire. Their design prevents regional inspiration but facilitates expiration and secretion drainage. Regionalized lung volume reduction may occur through progressive deflation and absorption atelectasis.

The two most studied valve systems have similar characteristics. The valves expand to fill the airway lumen and are available in multiple diameters designed to occlude airways ranging from approximately 4–8.5 mm in diameter. Expiratory gas and secretions escape around the outside edges of the flexible Spiration valve (Spiration Incorporated (Redmond, Washington) and through the valve lumen of the Zephyr valve (Emphasys Medical (Redwood City, CA., Pulmonx Inc., Redwood City CA). The Spiration Intrabronchial Valve® system has an “umbrella design” in which an occlusive cover is stretched over a titanium wire frame. The Emphasys EBVR is a biocompatible cylindrical device with a “duck bill” one-way valve seated in a nitinol wire cage. Both are easily removable if the need arises.

Analysis of the first 98 patients who underwent BLVR with Emphasys endobronchial valves at 9 international centers reported small but significant improvements in FEV₁, FVC, RV and 6 MWD. (38) In the first 90 days, eight patients had serious complications including 1 non-procedural death in a patient with prior lobectomy secondary to lung cancer, 3 pneumothoraces requiring surgical intervention, and 4 air leaks lasting > 7 days. Minor complications included COPD exacerbations in 17 patients. Physiologic improvement was most pronounced in the subset (n=70) who achieved complete lobar exclusion. Change from baseline to 90-day assessment in FEV₁ and 6MWD were significantly greater post-treatment in those who achieved complete lobar exclusion vs. those who did not: 14.0 ± 29.3% vs. 3.2

$\pm 15.7\%$ change in FEV₁ ($p=0.02$) and 13.9 ± 45.5 meters vs. 26.7 ± 58.8 meters change in 6 MWD ($p=0.001$).

The Spiration system Intrabronchial Valve® phase II trial (IBV) assessed safety in a multicenter pilot study that treated 91 patients with severe obstruction, hyperinflation and predominantly upper lobe emphysema with 609 valves placed bilaterally in upper-lobe segmental or subsegmental bronchi (mean 6.7 valves, median of 6 valves per patient).⁽²⁹⁾ Valves were placed in the desired airways with 99.7 % technical success and no evidence of migration or airway wall erosion. There were no reported procedural deaths and 30 day morbidity and mortality was 5.5 and 1.1%, respectively. Significant improvements in SGRQ quality of life at 6 months post implantation were reported (-8.2 ± 16.2 , $p=0.001$). Improvements in quality of life correlated with a decrease in lung volume (-294 ± 427 ml, $p=0.007$) in treated lobes without visible atelectasis. FEV₁, 6 MWD and lower extremity ergometry testing did not significantly change post IBV implantation. A quantitative CT analysis of lung volume changes in 57 subjects before and after IBV endobronchial valve implantation of the treated and non treated lobes was reported.⁽³⁹⁾ Treated upper lobes had a decrease in volume (335 ± 444 ml) in 88% of the cohort while untreated lobes had a simultaneous 11.6% increase in volume. The regional changes in lung volume were associated with clinically important improvements in quality of life (SGRQ, -8.95 ± 16.22) but not clinically important changes in lung function tests. The mechanisms for improvements in quality of life with the redistribution in ventilation following IBV treatment are unexplained at present and require further study.

Phase III Endobronchial One-Way Valve Trials

The VENT (Endobronchial Valve for Emphysema Palliation Trial) is the first prospective randomized multi-center trial to evaluate BLVR using the Zephyr endobronchial valve (Emphasys Medical Inc., Redwood City, CA) compared to medical care in patients with severe heterogeneous emphysema.⁽²⁸⁾

VENT randomized 321 patients (aged 40–75) to implantation with endobronchial valves ($n=220$) or to medical management ($n=101$) as defined by the GOLD 2001 guidelines. The primary efficacy endpoints were percent changes in FEV₁ and 6 MWD at 6 months compared to baseline for each group analyzed by intention to treat. Secondary endpoints included mean changes in quality of life as assessed by SGRQ, incremental cycle exercise capacity, dyspnea measured by a modified Medical Research Council score (mMRC), the amount of target lobe volume reduction measured by quantitative HRCT, and daily oxygen usage. The primary safety endpoint was a difference between the two groups in a Major Complication Composite (MCC) rate at 180 days post randomization. The MCC included death, massive hemoptysis, empyema, pneumonia distal to valves and ventilator dependency ≥ 24 hours. Prior to randomization, all patients underwent 6–8 weeks of outpatient pulmonary rehabilitation and optimization of their medical management at the discretion of the treating physician per GOLD guidelines. High resolution chest CT (HRCT) was performed at baseline and 180 days post randomization. HRCT images were analyzed at a core lab to provide quantitative and visual indices of lobar emphysema severity and fissure integrity to determine patient eligibility and lung structural characterization. HRCT scans were used to target treatment; the lobe with the highest percent of emphysema and greatest degree of heterogeneity (difference in % emphysema between ipsilateral lung lobes) was selected for EBV treatment.

Conscious sedation (71.5% patients) or general anesthesia (28.5% patients) were used to place the valves in a single lobe using flexible bronchoscopy alone (98.6%) or in combination with rigid bronchoscopy. The mean number of valves placed in the targeted lobe was 3.8 per subject (range 1–9). Mean procedure time was 33.8 ± 20.5 minutes. The

lobes targeted for EBV included: right upper lobe (52.3%), right lower lobe (9.3), left upper lobe (24.3%) and left lower lobe (14.0%).

At 6 months post randomization the FEV₁ increased 4.3% in the EBV group while it decreased 2.5% in the control group; thus FEV₁ was a mean of 6.8% greater post treatment following EBV compared to the control group (p=0.005). At 6 months 6 MWD increased 2.6% in the EBV group and decreased 3.2% in the medical group; thus there was a mean increase of 5.8% for 6 MWD following EBV compared to medical therapy (p=0.04). The secondary outcomes also showed modest improvements at 6 months following EBV therapy in comparison to medical treatment. In this regard, supplemental oxygen use was slightly less in the EBV group (P=0.005) and SGRQ differed by a mean of -3.4 (p=0.04), mMRC by -0.3 (p=0.04), and cycle ergometry peak workload by 3.8 watts (p=0.05), all favoring EBV over medical therapy alone.

At 6 months, medically treated patients had a MCC rate of 1.2% compared to a rate of 6.1% in EBV subjects. Included in the MCC at 6 months was a 2.8% mortality rate in the EBV group vs. no deaths in the controls (p=0.19). Pneumonia developed distal to the EBV valve in 4.2% of EBV subjects, all pneumonias resolved with antibiotic therapy. Hemoptysis occurred in 5.6 % of EBV subjects over 6 months post implantation and in no controls (p=0.02). Hemoptysis was most likely due to oozing from granulation tissue at the implantation site. COPD exacerbations requiring hospitalization occurred more commonly following EBV (7.9%) vs. controls (1.2%), p < 0.03. In 12 months of follow-up, 31 patients had valves removed; reasons for this included retrieval of migrated valve (n=8), patient's request (n=7), pneumonia distal to valve (n=3), placement in the incorrect lobe (n=3), recurring COPD exacerbations (n=2), and hemoptysis (n=1).

Heterogeneity (difference in the % of emphysema between lobes in the treated lung) and fissure integrity proved to be predictive in determining the magnitude of improvements in FEV₁ and 6 MWD. The enhancing effect of heterogeneity on changes in FEV₁ and 6 MWD was significant within any quartile of emphysema % and overall was greater with increasing degrees of heterogeneity (Figure 6). At a 15% median cutoff, the high heterogeneity subgroup had relatively greater improvements in FEV₁ and 6 MWD at 6 months follow-up. EBV subjects with intact fissures had incremental improvements in FEV₁ at 6 months of 16.2% (p<0.001) and 17.9% at 12 months (p<0.001) in comparison to those with incomplete fissures that had insignificant changes of 2% and 2.8% at 6 and 12 months, respectively.

EBV subjects also had a greater reduction in quantitative treated lobe volume, as assessed by HRCT, at 6 months compared with medically treated controls (-378.4 vs. -16.3 ml, p<0.002), an effect that was further enhanced in the setting of complete fissures (-712.5 vs. +2.2 ml, p<0.001). Targeted lobe volume reduction measured by HRCT correlated inversely with the change in FEV₁ (r=-0.53, p<0.001).

Emphasys received expedited FDA review for the "Zephyr" endobronchial valve and their application was denied FDA approval in December 2008. The panel commented that the mean changes in FEV₁ and 6 MWD were not clinically meaningful and that additional data regarding long-term safety of the device was needed. Emphasys dissolved as a company 8 weeks later and the Zephyr valve was purchased by Pulmonx Inc., Palo Alto CA. Plans for future investigation using the Zephyr valve are being developed but hopefully will utilize the patient characteristics that were identified by VENT (e.g., high heterogeneity, intact fissures and complete lobar exclusion) to be associated with clinically meaningful improvements.

The Spiration Intrabronchial Valve (IBV®) system is currently enrolling patients in a pivotal phase III study.

Lung Volume Reduction via Biological Remodeling of Emphysematous Tissue

Biological lung volume reduction is a process in which a biodegradable sclerosant gel (BioLVR, Aeris Therapeutics Inc., Woburn, MA) is used to polymerize the small airways and alveolar airspace.(25, 26) The fibrin-based hydrogel contains fibroblast growth factor-1 complexed with chondroitin sulfate. Focal lung volume loss occurs as collapse, remodeling and scarring take place over a period of weeks. A theoretical advantage of this method of lung reduction is that it induces its effects distally at the small airway and alveolar level and may work even in the presence of collateral ventilation.

In an open labeled, multicenter phase 2 dose-ranging study, BioLVR Hydrogel was administered to 8 subsegmental sites (4 pulmonary subsegments in each upper lobe) involving: 1) low dose (n = 28) with 10 mL per site (LD); and 2) high dose treatments (n=22) with 20 mL per site (HD). (40) Safety was assessed by the incidence of serious medical complications that followed treatment. Efficacy was assessed by changes from baseline in lung function, dyspnea score, 6 MWD, and quality of life. There were no deaths and the 4 serious treatment-related complications all resolved with medical treatment. A reduction in RV/TLC at 12-weeks (primary efficacy outcome) was reported with both LD ($-6.4 \pm 9.3\%$, $p=0.002$) and HD ($-5.5 \pm 9.4\%$, $p=0.028$) treatments. Improvements in lung function at 6 months were greater with HD ($FEV_1 +15.6\%$ ($p=0.002$), $FVC +9.1\%$ ($p=0.034$)) than with LD ($FEV_1 +6.7\%$ ($p=0.021$), $FVC +5.1\%$ ($p=0.139$)). LD and HD treated groups both demonstrated improved symptom scores and health related quality of life (HRQOL). Overall the improvement was larger, and responses more durable with 20 mL/site than 10 mL/site dosing.

BioLVR was also administered to 25 patients with homogeneous emphysema in an open label phase II study; 8 subjects received low dose (LD) treatment with 10 ml per site at 8 subsegments and 17 received high dose (HD) treatment with 20 ml per site at 8 subsegments. (41) There were no deaths or serious medical complications from study treatment. A statistically significant reduction in air trapping was seen at 3 months follow-up in HD patients but not LD patients. At 6 months, changes from baseline in FEV_1 , FVC, RV/TLC, dyspnea scores and SGRQ were better with HD than LD treatment, but only attained statistical significance in HD for FEV_1 ($+13.8 \pm 20.2$, $p=0.007$), dyspnea (-0.8 ± 0.7 m MRC score, $p=0.001$) and SGRQ total score (-12.2 ± 12.3 , $p=0.0001$)

Aeris Therapeutics notified participating clinical investigative sites in November 2008 that planning of a phase III trial of BioLVR was being halted and the company moved towards development of a new polymeric sealant named AeriSeal™.(42) AeriSeal is currently undergoing active investigation in Europe. Preliminary data presented in 15 patients with upper lobe predominant emphysema treated in 2–4 subsegments showed a reduction in CT measured lung volume in treated lobes and an increase in ipsilateral volume in non-treated lobes. The reductions in lobar volume correlated with a reduction in gas trapping (RV/TLC, $r=0.59$, $p=0.02$), increased FEV_1 ($r=-0.65$, $p=0.009$) and 6 MWD ($r=0.48$, $p=0.07$). Future prospective randomized controlled phase III trials with AeriSeal™ are planned.

Airway Bypass Tract

Airway bypass transbronchial fenestration is a bronchoscopic technique using a needle tipped catheter designed to create extra-anatomic bronchial fenestrations that are maintained open with drug-eluting stents (Broncus Technologies, Mountain View, CA). Compared to normal lungs, emphysematous lungs may develop extensive collateral ventilation; gas moves from one lung region to another through non-anatomic pathways. (43) Through these collateral pathways, gas communicates between lung lobules and even lobes when incomplete fissures are present. Resistance through collateral circuits is usually less than

through the bronchial tree. Bronchial fenestrations create a low resistance extra-anatomic airflow tract that facilitates ventilation in targeted areas of emphysema. Bronchial fenestrations may decrease hyperinflation by enhancing the emptying of gas trapped in emphysematous tissue and thereby potentially improve exercise tolerance and quality of life.

With this method a flexible bronchoscope is inserted to the level of the segmental bronchus and a Doppler probe is used to localize and avoid lung blood vessels. Transbronchial openings are created with a 25-gauge transbronchial needle-tipped catheter and a 2.5 mm balloon dilator. An expandable silicone coated, 3 by 3 mm stainless steel stent is inserted and anchored within the bronchial wall.(44–46) Early efficacy data are based upon an ex-vivo trial on explanted human lungs and animal studies.(47) In early animal trials, stent stenosis limited stent function, a problem partially overcome by adding anti-proliferative drugs to the stents. A randomized trial demonstrated the superior efficacy of weekly bronchoscopic applications of topical mitomycin C versus saline in maintaining stent patency in dogs.(45) A randomized trial of paclitaxel-eluting vs. non-drug eluting stents in a canine model showed 12 week patency rates of 65% vs. 0% and an absence of paclitaxel-related toxicity.(48)

The safety and clinical results of a multicenter evaluation of airway bypass with paclitaxel-eluting stents for 35 patients with severe bilateral emphysema have been published. (46) All had post-bronchodilator residual volume (RV) $\geq 220\%$ of predicted, total lung capacity (TLC) $\geq 133\%$ of predicted and FEV₁ $< 40\%$ of predicted, and all but two patients had homogeneously distributed emphysema. A median of 8 stents (range 2–12) were inserted bilaterally in each upper and lower lobe. Standard pulmonary function parameters, 6MWD, dyspnea as measured by modified Medical Research Council (mMRC) scale, and SGRQ scores were assessed in follow-up. At 6 months, there were statistically significant reductions from post-rehabilitation baseline in RV [5.34 ± 1.13 L to 4.98 ± 1.25 L ($p=0.04$)] and dyspnea (-0.5 ; $p = 0.025$) but no changes in TLC, FVC, FEV₁, 6MWD and SGRQ. A subgroup analysis of patients above and below the RV/TLC median of 0.67 demonstrated a significant reduction in RV (-0.87 L; $p=0.022$) and increases in FVC (11.1%; $p = .026$) and 6MWD (28.6 m, $p = .021$) in the more severely gas trapped group at 1 month. However none of the benefits were maintained at 6 months. One patient died as a result of intra-operative airway bleeding, resulting in a Drug Safety Monitoring Board investigation and procedural modifications. Other serious adverse events related to the procedure included intraoperative pneumomediastinum (5.3%), COPD exacerbation (32.4%) and respiratory infection (27%). Bronchoscopic inspection of 26 stents at 6 months demonstrated a patency rate of 69%.

Broncus® (Mountain View, CA) recently announced the results of a phase III double blinded, randomized, sham-controlled trial (EASE) of the airway bypass procedure using the Exhale drug-eluting stent.(49) EASE was designed to demonstrate safety and efficacy of the procedure, but it failed to meet its composite primary endpoint of improving both FVC and mMRC dyspnea score when compared to sham controls. mMRC dyspnea score alone, however, did show significant improvement after the airway bypass procedure. Post hoc analysis of patients who met the composite primary endpoint showed that a reduction in RV ≥ 500 ml post treatment and at 1 month correlated with significant improvements in lung function and symptoms, while such improvements were not seen in those achieving lesser degrees of reduction in RV. At this date, peer review publication of the EASE results is pending.

Other LVR Techniques

Several other promising techniques to achieve lung volume reduction have recently been described in small numbers of patients. These techniques vary significantly in their approach

but share the common feature of not being affected by the presence of collateral ventilation. In a pilot study, lung volume reduction coils (PneumRx, Inc.; Mountain View, CA) were bronchoscopically placed into the most diseased areas of lung bilaterally to achieve lung tissue compression.(50) Safety was the primary endpoint and efficacy outcomes were secondary endpoints in the 11 severe emphysema patients (8 homogeneous, 3 heterogeneous) that were studied. The 11 patients underwent 21 treatments with a total of 101 coils placed. A total of 33 adverse events were reported; none were severe, 64% were moderate, and 36% were mild. Adverse events possibly attributed to the procedure or device included dyspnea (10 events), cough (5 events), COPD exacerbations (3 events) and chest pain (1 event). Improvements in FEV₁, RV, TLC, SGRQ and 6 MWD were observed at one and three months following the first procedure. The greatest relative changes were observed in 6 MWD, SGRQ and mMRC in the patients with heterogeneous emphysema. Further testing of the device is ongoing.

The technique of bronchial thermal vapor ablation (BTVA; Uptake Medical Corp., Seattle), involves the bronchoscopic application of thermal energy to targeted areas of emphysema..(51) BTVA induced-injury triggers an inflammatory response in the airway and parenchyma, thereby producing lung volume reduction. BTVA utilizes a vapor generator and metal balloon vapor catheter, with target dosing at 3–7.5 cal/g according to a prior CT based tissue-air algorithm. In a pilot study, 11 patients with heterogeneous emphysema, mean FEV₁ of 0.77±0.17 L (32% predicted) and RV of 4.1±0.9 L (219% predicted), underwent 9 right and 2 left upper lobe unilateral treatments (approximately 3 applications/lobe). Immediate mild opacification in the target areas was demonstrated by chest x-ray in all patients. All patients were discharged 24–48 hours post procedure. Serious adverse events requiring hospitalization occurred in 5 patients; two patients had exacerbations of COPD and three patients had probable bacterial pneumonia, anxiety, and atrial tachycardia, respectively. Minor adverse events not requiring hospitalization included minor hemoptysis (n=6) and inflammatory pneumonitis (n=2). All patients had less dyspnea at 3–16 weeks post-procedure. Seven patients completed 1-month follow-up with a mean increase in FEV₁ of 9±8% and decrease in RV of 7.4±9%. However, at 6 months there was no difference compared to baseline in FVC, FEV₁, 6 MWD and RV. In contrast, MRC dyspnea score (2.6 baseline to 2.1 at 6 months) and SGRQ (64.4 baseline to 49.1 at 6 months) both improved after BTVA. BTVA continues to undergo further investigation as a potential therapy for LVR at this time.

External placement of modified chest tubes into emphysematous regions produced increases in FEV₁ and 6 MWD and reductions in RV, TLC, mMRC and SGRQ in 3 patients.(52) These data support the concept that placing artificial spiracles into diseased emphysematous lung could enhance gas emptying, decrease end-expiratory lung volume and potentially ameliorate the consequences of hyperinflation.

Finally, the presence of collateral ventilation is an important limitation to the success of endobronchial valve treatment.(53) A new system (Chartis, Pulmonx, Inc., Palo Alto, CA) is now available that consists of a console and balloon-tipped catheter that can be placed through the working channel of a bronchoscope to measure flow and pressures from isolated lung regions on a lobar to sub-segmental level. During assessment, the balloon is inflated, the airway and lung region of interest are isolated and airflow and pressure are measured. The absence of airflow during balloon occlusion signifies the lack of collateral ventilation and may help target appropriate emphysema patients and lung regions for endobronchial valve treatment. This device is currently being used in small pilot studies to optimize the selection of patients for endobronchial valve treatment.

Summary

Hyperinflation is a major cause of morbidity and mortality in severe emphysema. LVRS offers a select group of emphysema patients the opportunity for clinically meaningful improvements in exercise tolerance, lung function, quality of life, and in those with upper lobe predominant disease and low exercise, survival. A variety of novel, less invasive bronchoscopic techniques are currently undergoing study and show promise to effectively produce lung reduction in a broader group of patients with advanced emphysema. Additional well designed prospective studies are needed to determine the optimum role of LVRS vs. bronchoscopic LVR in the treatment of severe emphysema. (54)

References

1. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* Nov; 1998 158(5 Pt 1):1557–65. [PubMed: 9817708]
2. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* Sep 1; 2001 164(5):770–7. [PubMed: 11549531]
3. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med.* Mar; 1997 155(3):906–15. [PubMed: 9117025]
4. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* Mar 15; 2005 171(6):591–7. [PubMed: 15591470]
5. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med.* Jan 21; 2010 362(3):217–27. [PubMed: 20089972]
6. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: Role of hyperinflation. *Chest.* Jul; 2010 138(1):32–8. [PubMed: 20190002]
7. Criner GJ. COPD and the heart: When less lung means more heart. *Chest.* Jul; 2010 138(1):6–8. [PubMed: 20605807]
8. Mineo D, Ambrogi V, Cufari ME, Gambardella S, Pignotti L, Pompeo E, et al. Variations of inflammatory mediators and alpha1-antitrypsin levels after lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med.* Apr 15; 2010 181(8):806–14. [PubMed: 20056899]
9. Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg.* Jan; 1995 109(1):106–16. discussion 116–9. [PubMed: 7815786]
10. McKenna RJ Jr, Brenner M, Gelb AF, Mullin M, Singh N, Peters H, et al. A randomized, prospective trial of stapled lung reduction versus laser bullectomy for diffuse emphysema. *J Thorac Cardiovasc Surg.* Feb; 1996 111(2):317–21. discussion 322. [PubMed: 8583804]
11. Bingisser R, Zollinger A, Hauser M, Bloch KE, Russi EW, Weder W. Bilateral volume reduction surgery for diffuse pulmonary emphysema by video-assisted thoracoscopy. *J Thorac Cardiovasc Surg.* Oct; 1996 112(4):875–82. [PubMed: 8873712]
12. Cooper JD, Patterson GA, Sundaresan RS, Trulock EP, Yusef RD, Pohl MS, et al. Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. *J Thorac Cardiovasc Surg.* Nov; 1996 112(5):1319–29. discussion 1329–30. [PubMed: 8911330]
13. Miller JJ Jr, Lee RB, Mansour KA. Lung volume reduction surgery: Lessons learned. *Ann Thorac Surg.* May; 1996 61(5):1464–8. discussion 1468–9. [PubMed: 8633960]
14. Daniel TM, Chan BB, Bhaskar V, Parekh JS, Walters PE, Reeder J, et al. Lung volume reduction surgery. case selection, operative technique, and clinical results. *Ann Surg.* May; 1996 223(5):526–31. discussion 532–3. [PubMed: 8651743]

15. Argenziano M, Moazami N, Thomashow B, Jellen PA, Gorenstein LA, Rose EA, et al. Extended indications for lung volume reduction surgery in advanced emphysema. *Ann Thorac Surg.* Dec; 1996 62(6):1588–97. [PubMed: 8957356]
16. Wisser W, Tschernko E, Senbaklavaci O, Kontrus M, Wanke T, Wolner E, et al. Functional improvement after volume reduction: Sternotomy versus videoendoscopic approach. *Ann Thorac Surg.* Mar; 1997 63(3):822–7. discussion 827–8. [PubMed: 9066408]
17. Health Care Financing Administration: Report to Congress. Lung volume reductionsurgery and medicare coverage policy: Implications of recently published evidence. DHHS. 1998
18. NETT Research Group. Rationale and design of the national emphysema treatment trial, A prospective randomized trial of lung volume reduction surgery. *Chest.* 1999; 116:1750. [PubMed: 10593802]
19. Kolata, G. Medicare says it will pay but patients say “No thanks”. *New York Times*; March 3. 2006
20. Grady, D. After early success, operations to remove damaged tissues have fallen sharply. *New York Times*; Nov. 29. 2007
21. Toma TP, Hopkinson NS, Hillier J, Hansell DM, Morgan C, Goldstraw PG, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. *Lancet.* Mar 15; 2003 361(9361):931–3. [PubMed: 12648974]
22. Watanabe Y, Matasuo K, Tamaoki A, Komoto R, Hiraki S. Bronchial occlusion with endobronchial watanabe spigot. *J Bronchol.* 2003; 10:264–7.
23. Sabanathan S, Richardson J, Pieri-Davies S. Bronchoscopic lung volume reduction. *J Cardiovasc Surg (Torino).* Feb; 2003 44(1):101–8.
24. Rendina EA, De Giacomo T, Venuta F, Coloni GF, Meyers BF, Patterson GA, et al. Feasibility and safety of the airway bypass procedure for patients with emphysema. *J Thorac Cardiovasc Surg.* Jun; 2003 125(6):1294–9. [PubMed: 12830047]
25. Ingenito EP, Reilly JJ, Mentzer SJ, Swanson SJ, Vin R, Keuhn H, et al. Bronchoscopic volume reduction: A safe and effective alternative to surgical therapy for emphysema. *Am J Respir Crit Care Med.* Jul 15; 2001 164(2):295–301. [PubMed: 11463604]
26. Ingenito EP, Berger RL, Henderson AC, Reilly JJ, Tsai L, Hoffman A. Bronchoscopic lung volume reduction using tissue engineering principles. *Am J Respir Crit Care Med.* Mar 1; 2003 167(5):771–8. [PubMed: 12406835]
27. Snell GI, Holsworth L, Borrill ZL, Thomson KR, Kalff V, Smith JA, et al. The potential for bronchoscopic lung volume reduction using bronchial prostheses: A pilot study. *Chest.* Sep; 2003 124(3):1073–80. [PubMed: 12970040]
28. Sciruba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med.* Sep 23; 2010 363(13):1233–44. [PubMed: 20860505]
29. Serman DH, Mehta AC, Wood DE, Mathur PN, McKenna RJ Jr, Ost DE, et al. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration.* 2010; 79(3):222–33. [PubMed: 19923790]
30. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* May 22; 2003 348(21):2059–73. [PubMed: 12759479]
31. Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the national emphysema treatment trial research group. *Ann Thorac Surg.* Aug; 2006 82(2):431–43. [PubMed: 16888872]
32. DeCamp MM, Blackstone EH, Naunheim KS, Krasna MJ, Wood DE, Meli YM, et al. Patient and surgical factors influencing air leak after lung volume reduction surgery: Lessons learned from the national emphysema treatment trial. *Ann Thorac Surg.* Jul; 2006 82(1):197–206. discussion 206–7. [PubMed: 16798215]
33. National Emphysema Treatment Trial Research Group. Safety and efficacy of median sternotomy versus video-assisted thoracic surgery for lung volume reduction surgery. *J Thorac Cardiovasc Surg.* 2004; 127:1350–60. [PubMed: 15115992]

34. Ramsey SD, Berry K, Etzioni R, Kaplan RM, Sullivan SD, Wood DE, et al. Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema. *N Engl J Med*. May 22; 2003 348(21):2092–102. [PubMed: 12759480]
35. Ramsey SD, Shroyer AL, Sullivan SD, Wood DE. Updated evaluation of the cost-effectiveness of lung volume reduction surgery. *Chest*. Mar; 2007 131(3):823–32. [PubMed: 17356099]
36. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med*. Oct 11; 2001 345(15):1075–83. [PubMed: 11596586]
37. Naunheim KS, Wood DE, Krasna MJ, DeCamp MM Jr, Ginsburg ME, McKenna RJ Jr, et al. Predictors of operative mortality and cardiopulmonary morbidity in the national emphysema treatment trial. *J Thorac Cardiovasc Surg*. Jan; 2006 131(1):43–53. [PubMed: 16399293]
38. Wan IY, Toma TP, Geddes DM, Snell G, Williams T, Venuta F, et al. Bronchoscopic lung volume reduction for end-stage emphysema: Report on the first 98 patients. *Chest*. Mar; 2006 129(3):518–26. [PubMed: 16537847]
39. Coxson HO, Nasute Fauerbach PV, Storness-Bliss C, Muller NL, Cogswell S, Dillard DH, et al. Computed tomography assessment of lung volume changes after bronchial valve treatment. *Eur Respir J*. Dec; 2008 32(6):1443–50. [PubMed: 18684848]
40. Criner GJ, Pinto-Plata V, Strange C, Dransfield M, Gotfried M, Leeds W, et al. Biologic lung volume reduction in advanced upper lobe emphysema: Phase 2 results. *Am J Respir Crit Care Med*. May 1; 2009 179(9):791–8. [PubMed: 19179484]
41. Refaely Y, Dransfield M, Kramer MR, Gotfried M, Leeds W, McLennan G, et al. Biologic lung volume reduction therapy for advanced homogeneous emphysema. *Eur Respir J*. Jul; 2010 36(1):20–7. [PubMed: 19926742]
42. Magnussen H, Kirsten A, Eberhardt R, Schmidt B, Behr J, Stanzel F, Bonnet R, Herth FJ. CT assessment of regional lung volume changes following endobronchial volume reduction therapy in emphysema patients using a synthetic adhesive hydrogel-foam. *Am J Respir Crit Care Med*. 2010; 181:A5533.
43. Fessler HE. Collateral ventilation, the bane of bronchoscopic volume reduction. *Am J Respir Crit Care Med*. Mar 1; 2005 171(5):423–4. [PubMed: 15722418]
44. Choong CK, Haddad FJ, Gee EY, Cooper JD. Feasibility and safety of airway bypass stent placement and influence of topical mitomycin C on stent patency. *J Thorac Cardiovasc Surg*. Mar; 2005 129(3):632–8. [PubMed: 15746748]
45. Choong CK, Haddad FJ, Gee EY, Cooper JD. Feasibility and safety of airway bypass stent placement and influence of topical mitomycin C on stent patency. *J Thorac Cardiovasc Surg*. Mar; 2005 129(3):632–8. [PubMed: 15746748]
46. Cardoso PF, Snell GI, Hopkins P, Sybrecht GW, Stamatis G, Ng AW, et al. Clinical application of airway bypass with paclitaxel-eluting stents: Early results. *J Thorac Cardiovasc Surg*. Oct; 2007 134(4):974–81. [PubMed: 17903516]
47. Lausberg HF, Chino K, Patterson GA, Meyers BF, Toeniskoetter PD, Cooper JD. Bronchial fenestration improves expiratory flow in emphysematous human lungs. *Ann Thorac Surg*. Feb; 2003 75(2):393–7. discussion 398. [PubMed: 12607646]
48. Choong CK, Phan L, Massetti P, Haddad FJ, Martinez C, Roschak E, et al. Prolongation of patency of airway bypass stents with use of drug-eluting stents. *J Thorac Cardiovasc Surg*. Jan; 2006 131(1):60–4. [PubMed: 16399295]
49. Broncus Technologies Inc.. Broncus reports early EASE trial results for airway bypass with EXHALE drug-eluting stents. 2009. <http://markets.hpcwire.com/taborcomm.hpcwire/?guid=1081574>
50. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. Bronchoscopic lung volume reduction with a dedicated coil: A clinical pilot study. *Ther Adv Respir Dis*. Aug; 2010 4(4):225–31. [PubMed: 20538661]
51. Snell GI, Hopkins P, Westall G, Holsworth L, Carle A, Williams TJ. A feasibility and safety study of bronchoscopic thermal vapor ablation: A novel emphysema therapy. *Ann Thorac Surg*. Dec; 2009 88(6):1993–8. [PubMed: 19932274]

52. Saad R, Neto V, Botter M, Stirbulov R, Rivaben J, Goncalves R. Therapeutic application of collateral ventilation with pulmonary drainage in the treatment of diffuse emphysema: Report of the first three cases. *J Bras Pneumol*. 2009; 1(1):14–9.
53. Ernst A, Eberhardt R, Gompelmann D, Herth FJ. Low degree of collateral ventilation measurement in heterogeneous emphysema subject treated by endobronchial lung volume reduction predicts ELVR success. *Am J Respir Crit Care Med*. 2010; 181:A1571.
54. Criner GJ. Endoscopic interventions in severe emphysema. *Am J Respir Crit Care Med*. 2009; 180:684. [PubMed: 19762593]

Figure 1.

Probability of death as a function of the number of months after randomization (Kaplan-Meier estimates). High risk patients were defined as $FEV_1 \leq 20\%$ predicted and either homogeneous emphysema or $DL_{CO} \leq 20\%$ predicted. Low baseline exercise capacity was defined as a maximal workload at or below the sex-specific 40th percentile (25 W for women and 40 W for men); high exercise capacity was defined as a workload above this threshold. P values were derived by Fisher's exact test for the comparison between groups over a mean follow-up period of 29.2 months. (with permission,(30))

Figure 2.

Changes from post rehabilitation baseline in exercise capacity (maximal workload), percentage of predicted FEV₁, six minute walk distance, health-related quality of life (St George's Respiratory Questionnaire), quality of life (Quality of Well-Being Scale), and dyspnea (UCSD Shortness of Breath Questionnaire) after 6, 12, and 24 months of follow-up for all patients shown in the first, second and third rows of data, respectively. The category Missing includes: patients too ill to complete the procedure, or who declined to complete the procedure but did not explain why. For the Quality of Well-Being Scale, patients who died were assigned a score of 0 for the visit, and patients who did not complete the questionnaire were assigned a score equal to half the lowest score observed for the visit. The degree to which the bars are shifted to the upper left of the chart indicates the degree of relative benefit of LVRs over medical treatment. The percentage shown in each quadrant is the percent of patients in the specified treatment group with a change in the outcome falling in that quadrant. P-values were determined by the Wilcoxon rank-sum test. (With permission, (30)).

Figure 3.

Kaplan-Meier estimates of the cumulative probability of death as a function of years post randomization to LVRs (gray line) or medical therapy (black line) for (a) all patients and (b–d) non high risk and upper lobe predominant subgroups of patients. The P-value is from the Fishers exact test for difference in the proportions of patients who died during the 4.3 years (median) of follow-up. Shown below each graph are the numbers of patients at risk, the Kaplan-Meier probabilities, the ratio of the probabilities (LVRs:Medical), and P-value for the difference in these probabilities. This is an intention-to-treat analysis. (a) All patients (N=1218). (b) Non-high-risk patients (N=1078). (c) Upper-lobe predominant and low baseline exercise capacity (N=290). (d) Upper-lobe predominant and high exercise capacity (N=419). (RR = relative risk). (with permission,(31))

Figure 4.

Improvement in exercise capacity (increase in maximum work of > 10 watts above the patient's post-rehabilitation baseline) at 1, 2, and 3 years post randomization to LVRS (open box) or medical therapy (filled box) for (a) all patients and (b–d) non high risk and upper lobe predominant patient subgroups. Shown below each graph are the numbers of patients evaluated, the odds ratio for improvement (LVRS:Medical), and the Fishers exact P-value for difference in proportion improved. Patients who died or who did not complete the assessment were considered not improved. This is an intention-to-treat analysis. (a) All patients (N=1218). (b) Non high risk patients (N=1078). (c) Upper-lobe predominant and low baseline exercise capacity (N=290). (d) Upper-lobe predominant and high exercise capacity (N=419). (With permission,(31))

Figure 5.

Improvement in health-related quality of life (decrease in St George's Respiratory Questionnaire total score of > 8 units below the patient's post-rehabilitation baseline) at 1, 2, 3, 4, and 5 years after randomization to LVRS (open box) or medical therapy (filled box) for (a) All patients and (b–d) non high risk and upper lobe predominant subgroups of patients. Shown below each graph are the numbers of patients evaluated, the odds ratio for improvement (LVRS:Medical), and the Fisher's exact P-value for difference in proportion improved. Patients who died or who did not complete the assessment were considered not improved. This is an intention-to-treat analysis. (a) All patients (N=1218). (b) Non high risk patients (N=1078). (c) Upper-lobe predominant and low baseline exercise capacity (N=290). (d) Upper-lobe predominant and high exercise capacity (N=419). (With permission(31))

Figure 6.

Effect of heterogeneity on EBV response at 6 months. The effect of heterogeneity on change in FEV₁ (Panel A) and 6 MWD (Panel B) at 6 months after EBV implantation. % heterogeneity was the difference in quantitative emphysema score (the proportion of pixels of less than -910 Hounsfield units) between EBV treated and ipsilateral non-treated lobes. In Panel C, sagittal HRCT views with density mask views show low (6%, left subpanel) and high heterogeneity (25%, right subpanel). Darker areas represent pixels < -910 Hounsfield units, consistent with emphysema. (With permission, (28))

Table 1

Characteristics of all 1218 patients at baseline (with permission, {{431 Fishman, A. 2003}})

[illegible]

Table 2

Improvement in exercise capacity and health-related quality of life at 24 months (with permission, {{431 Fishman, A. 2003}})

Patients	Improvement in Exercise Capacity				Improvement in Health-Related Quality of Life			
	Surgery Group	Medical-Therapy Group	Odds Ratio	P Value	Surgery Group	Medical-Therapy Group	Odds Ratio	P Value
	no./total no. (%)				no./total no. (%)			
All patients	54/371 (15)	10/378 (3)	6.27	<0.001	121/371 (33)	34/378 (9)	4.90	<0.001
High-risk†	4/58 (7)	1/48 (2)	3.48	0.37	6/58 (10)	0/48	—	0.03
Other	50/313 (16)	9/330 (3)	6.78	<0.001	115/313 (37)	34/330 (10)	5.06	<0.001
Subgroups‡								
Predominantly upper-lobe emphysema								
Low exercise capacity	25/84 (30)	0/92	—	<0.001	40/84 (48)	9/92 (10)	8.38	<0.001
High exercise capacity	17/115 (15)	4/138 (3)	5.81	0.001	47/115 (41)	15/138 (11)	5.67	<0.001
Predominantly non-upper-lobe emphysema								
Low exercise capacity	6/49 (12)	3/41 (7)	1.77	0.50	18/49 (37)	3/41 (7)	7.35	0.001
High exercise capacity	2/65 (3)	2/59 (3)	0.90	1.00	10/65 (15)	7/59 (12)	1.35	0.61

* Improvement in exercise capacity in patients followed for 24 months after randomization was defined as an increase in the maximal workload of more than 10 W from the patient's postrehabilitation base-line value. Improvement in the health-related quality of life in patients followed for 24 months after randomization was defined as a decrease in the score on the St. George's Respiratory Questionnaire of more than 8 points (on a 100-point scale) from the patient's postrehabilitation base-line score. For both analyses, patients who died or who missed the 24-month assessment were considered not to have improvement. Odds ratios are for improvement in the surgery group as compared with the medical-therapy group. P values were calculated by Fisher's exact test. A low base-line exercise capacity was defined as a postrehabilitation base-line maximal workload at or below the sex-specific 40th percentile (23 W for women and 40 W for men); a high exercise capacity was defined as a workload above this threshold.

† High-risk patients were defined as those with a forced expiratory volume in one second (FEV₁) that was 20 percent or less of the predicted value and either homogeneous emphysema on computed tomography or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value.

‡ High-risk patients were excluded from the subgroup analyses. For improvement in exercise capacity, P for interaction=0.005; for improvement in health-related quality of life, P for interaction=0.03. These P values were derived from binary logistic-regression models with terms for treatment, subgroup, and the interaction between the two, with the use of an exact-score test with three degrees of freedom. Other factors that were considered as potential variables for the definition of subgroups included the base-line FEV₁, carbon monoxide diffusing capacity, partial pressure of arterial carbon dioxide, residual volume, ratio of residual volume to total lung capacity, ratio of expired ventilation in one minute to carbon dioxide excretion in one minute, distribution of emphysema (heterogeneous vs. homogeneous), perfusion ratio, score for health-related quality of life, and Quality of Well-Being score; age; race or ethnic group; and sex.

Table 3

Mortality among all patients and in subgroups (with permission, {{431 Fishman, A. 2003}})

Patients	90-Day Mortality			Total Mortality		
	Surgery Group	Medical Therapy Group	P Value	Surgery Group	Medical Therapy Group	P Value
	no. of deaths/total no. (%) (95% CI)			no. of deaths/total no. (%) (95% CI)		
All patients	48/608 (7.9) (6.9-9.0)	63/616 (10.2) (9.0-11.4)	<.001	137/608 (22.5) (20.4-24.6)	168/616 (27.3) (25.1-29.4)	<.001
High-risk†	28/79 (35.4) (24.4-46.4)	6/79 (7.6) (4.6-10.6)	<.001	42/79 (53.3) (41.3-65.3)	30/79 (38.0) (26.0-50.0)	<.001
Other	20/529 (3.8) (3.2-4.4)	57/537 (10.6) (9.6-11.6)	<.001	95/529 (18.0) (16.5-19.5)	138/537 (25.7) (23.9-27.5)	<.001
Subgroups‡						
Patients with predominantly upper-lobe emphysema						
Low exercise capacity	4/139 (2.9) (0.8-5.2)	1/111 (0.9) (0.1-1.7)	1.00	26/139 (18.7) (13.7-23.7)	13/111 (11.7) (7.7-15.7)	0.008
High exercise capacity	4/206 (1.9) (0.7-3.1)	2/133 (1.5) (0.3-2.7)	0.17	34/206 (16.5) (12.5-20.5)	19/133 (14.3) (10.3-18.3)	0.87
Patients with predominantly non-upper-lobe emphysema						
Low exercise capacity	7/84 (8.3) (4.3-12.3)	9/61 (14.7) (9.7-19.7)	0.02	28/84 (33.3) (25.3-41.3)	26/61 (42.6) (34.6-50.6)	0.04
High exercise capacity	11/109 (10.1) (7.1-13.1)	1/111 (0.9) (0.02-1.9)	0.003	27/109 (24.7) (19.7-29.7)	14/111 (12.6) (8.6-16.6)	0.002

* Mortality was measured from the date of randomization in both treatment groups. Total mortality rates are based on a mean follow-up of 28.2 months. P values were calculated by Fisher's exact test. Risk ratios are for the risk in the surgery group as compared with the risk in the medical therapy group. † Low baseline exercise capacity was defined as a pretest diffusion bronchovascular threshold or, as below the mean specific 400 percentile (21 W for women and 48 W for men); a high exercise capacity was defined as a workload above this threshold. ‡ Details specific to 400 percentile. § High-risk patients were defined as those with a forced expiratory volume in one second (FEV1) that was 20 percent or less of the predicted value and either homogeneous emphysema on computed tomography or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value. ¶ High-risk patients were excluded from the subgroup analyses. For total mortality, P for interaction=0.004; this P value was derived from binary logistic regression models with terms for treatment, subgroup, and the interaction between the two, with the use of an exact score test with three degrees of freedom. Other factors that were considered as potential variables for the definition of subgroups included the baseline FEV1, carbon monoxide diffusing capacity, partial pressure of arterial carbon dioxide, residual volume, ratio of residual volume to total lung capacity, ratio of expired ventilation to one minute to carbon dioxide retention in one minute, distribution of emphysema (heterogeneous vs. homogeneous), perfusion ratio, score for health-related quality of life, and Quality of Health-Related score, age, race, or ethnic group, and sex.

Table 4

Comparison of Investigational Bronchoscopic Lung Volume Reduction Techniques

Technique	Mechanism	Published PRCT Data	Reversibility of procedure	Affected by collateral ventilation
One-way endobronchial valves implanted into the airway	Promotes atelectasis by regionally blocking inspiration but allows expiration	Yes	Yes	Yes
Self activating coils placed into the airway	Induces atelectasis by assuming preformed coil shape & bends airway and collapses surrounding lung tissue	No	?	No
Targeted destruction and remodeling of emphysematous tissue	a. BioLVR - regional instillation of biological adhesives that collapse & remodel emphysematous regions b. BTVA heats & destroys targeted emphysematous tissue	No	No	No
Bypass tract airway stenting	Stents placed endobronchially into emphysematous tissue to enhance emptying of damaged lung tissue	Pending	Yes	No
Transpleural ventilation	Modified chest tubes are placed transthoracically into emphysematous tissue to empty damaged lung externally	No	Yes	No

Definition of Abbreviations: BioLVR, Biological lung volume reduction; BTVA, Bronchoscopic thermal vapour ablation