J Med Sci 2013;33(3):117-125
http://jms.ndmctsgh.edu.tw/3303117.pdf
DOI:10.6136/JMS.2013.33(3).117

Surgical and Bronchoscopic Lung Volume Reduction Interventions for Emphysema

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Emphysema is a common, chronic, progressively disabling and eventually fatal disease. The most debilitating clinical manifestations of emphysema are dyspnea and reduced exercise tolerance to a point where ordinary activities precipitate breathlessness. Emphysema is the fourth leading cause of death in the U. S with a steadily increasing incidence. In 2000 it was responsible for more than 100,000 deaths in the U.S and 2.4 million worldwide. The direct and indirect costs of providing health care for chronic obstructive pulmonary disease (COPD) were $26 billion in 1998, $30.4 billion in 2000 and an estimated $42.6 billion in 2007.[1]

Medical treatment of emphysema affords only modest symptomatic relief and it does not halt the relentless progression of the pathologic process. Proven beneficial treatments include smoking cessation, influenza vaccination, pulmonary rehabilitation, oral and inhaled bronchodilators and/or steroids. Only continuous supplemental oxygen in patients with documented hypoxemia has been shown to improve survival.[2,3]

During much of the last century, a variety of well intentioned but physiologically poorly conceived surgical interventions for emphysema were attempted. These included phrenic nerve crush, costochondrectomy, pneumoperitoneum, pleural scarification, pulmonary denervation and thoracoplasty.[4] Laforet[5] reviewed the outcomes of these operations and succinctly and sarcastically summarized this experience with the observation that "the alleged benefits of these maneuvers were frequently lost on patients whose worsening dyspnea left them with little energy to debate with their surgeons."

Effective surgical palliation for emphysema patients was first reported by Otto Brantigan in 1959.[6] Instead of restricting lung volume by altering the parietal chest cavity, he resected via a thoracotomy the most diseased portions of emphysematous lungs in an attempt to diminish the mismatch and thereby improve breathing mechanics and the function of the remaining organ. Many patients who survived the operation reported subjective improvement but the operative mortality was 18% and post-operative physiologic measurements were not obtained. Without objective outcomes the procedure was not widely accepted. Almost four decades later, Cooper *et al*. reintroduced pulmonary resection to treat emphysema. Bilateral "pneumectomy" or "reduction pneumoplasty" as he initially called it was accomplished using a median sternotomy, contemporary surgical techniques and longitudinal physiologic and functional assessments. He reported an operative mortality of 4.8% and significant improvements in symptoms, pulmonary function, exercise tolerance and quality of life (QOL) measures.[7] Similar results were reported by other groups in North America and Europe generating a wave of enthusiasm for what became known as lung volume reduction surgery (LVRS).[8-11]

Despite such encouraging outcomes, many clinicians were not convinced. More importantly major insurance payers denied payment for LVRS, labeling it as experimental therapy. Medicare analyzed outcomes from more than 700 of their beneficiaries who had undergone LVRS over 3 months in the mid 1990's. At 12 months after the procedure, 23% had died, and patients were three times more likely to have been hospitalized than in the prior year.[12] Based on this analysis, Medicare ceased reimbursement for LVRS in 1996, but agreed to partner with the National Heart, Lung and Blood Institute of the National Institutes for Health (NIH) to conduct a randomized trial of clinical efficacy and cost-effectiveness. The National Emphysema Treatment Trial (NETT) was born of this effort and began enrolling patients in 1999.[13] Within NETT, 1218 patients were randomized to LVRS versus maximal medical therapy at 17 different centers.[14] The study identified a subset (139 patients) with "high risk for death" from LVRS[15] and confirmed that LVRS confers durable symptomatic, physiologic and cost-effective improvement and for the first time demonstrated in a selected cohort a survival benefit when compared to optimal medical treatment (Figure 1).[16,17] However, the operation still carried a 5% 90-day mortality and was as-

Received: March 5, 2013; Accepted: March 8, 2013
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sociated with substantial perioperative pulmonary and cardiovascular morbidity.[18-21] The trial's strengths lie in its sizeable enrollment, robust multi-dimensional physiologic, radiographic and quality-of-life dataset, complete cost information and duration of follow-up. Data derived from NETT provides the best available evidence for the safety, efficacy, cost and durability of LVRS.[14,16,17,19]

Key words: lung volume reduction, emphysema

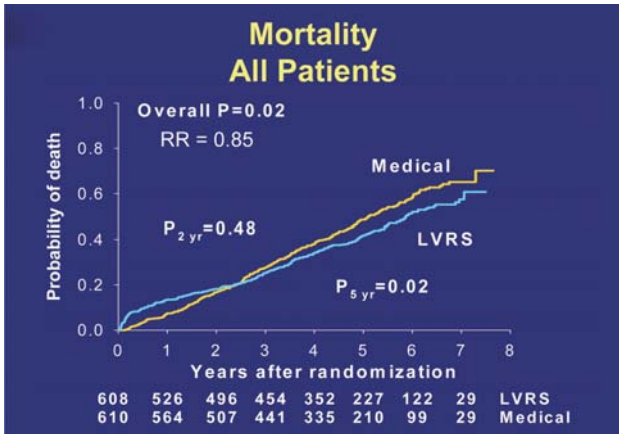

Fig. 1 Long-term mortality of all patients treated with LVRS versus maximal medical therapy in the National Emphysema Treatment Trial. Note the statistically significant (p=.02) reduction in relative risk of death (RR=0.85) for the surgical cohort.[17]

Patient selection and preparation

A successful LVRS program demands attention to the details of patient selection, preoperative preparation, intraoperative anesthetic and surgical technique and multidisciplinary post-operative care. Expertise in and effective communication between pulmonary medicine, thoracic surgery, thoracic anesthesia, pain management services, critical care medicine, respiratory therapy and rehabilitation medicine are vital components to any LVRS program.

NETT enrolled patients with a spectrum of physiologic impairment and varying anatomic phenotypes of emphysema distribution. The outcomes reported by NETT[14,17], Cooper[22] and others[23] suggest that the patients most likely to enjoy durable palliation have an upper lobe predominant and heterogeneous pattern of emphysema. NETT also defined a lower limit of impaired pulmonary function below which the mortality risk of LVRS was prohibitive. Patients with severely obstructive physiology (FEV1 < 20% predicted) combined with a depressed diffusion capacity (DLco < 20% predicted) and/or a homogenous pattern of emphysema had a 30-day mortality of 16%.[15] Contemporary inclusion and exclusion criteria for LVRS are presented in Table 1.[18,24] Utilizing such inclusion, exclusion and response data from NETT suggests that approximately 15% of patients with Global Obstructive Lung Disease (GOLD) stage III/IV emphysema may be candidates for LVRS.[25]

Given physiology and anatomy suitable for LVRS, most programs require candidates to complete 6 to 10-weeks of pulmonary rehabilitation before surgery. Smoking cessation is mandatory for all patients. During the period of rehabilitation, medical therapy for COPD must be optimized. This includes an assessment of supplemental oxygen needs at rest, with exercise and during sleep. Bronchodilator therapy needs to be optimized and the use of corticosteroids either orally or inhaled should be reduced or eliminated if possible. While pulmonary function tests did not improve, Reis and colleagues demonstrated statistically significant improvement in maximal work (cycle ergometry and 6-minute walk) and quality of life in NETT patients who completed pre-randomization pulmonary rehabilitation.[26] The efficacy of pre-operative rehabilitation has not been tested in a randomized fashion, but its use is widely felt to decrease post-operative morbidity, hasten recovery and is considered a clinical standard of care.

After completion of rehabilitation, patients should undergo a cardiopulmonary exercise test to allow assessment of risk and benefit. The NETT experience demonstrated that gender-adjusted performance during maximal exercise (cycle ergometry) allowed stratification of patients into low and high exercise capacity groups.[14] While the upper lobe predominant pattern alone predicted functional benefit following LVRS, patients with this radiologic pattern and a persistent low exercise capacity post-rehabilitation enjoyed a significant survival advantage as compared to similar patients randomized to continued medical therapy (Figure 2).[17]

LVRS Technique

Lung volume reduction can be accomplished by resection, plication or ablation of emphysematous targets. The availability of endomechanical surgical stapling de-

Table 1 Inclusion and Exclusion Criteria for LVRS

Inclusion Criteria

Radiographic evidence of emphysema especially involving upper lobes
Hyperinflation evidenced by:
TLC > 100% predicted and
RV > 150% predicted
FEV_1 > 20 and < 45 % predicted (post-bronchodilator)
DL_{CO} > 20 % predicted
Severe dyspnea
Restricted activities of daily living
Decreased quality of life
Abstinence from tobacco

Exclusion criteria

Active smoking
Bronchiectasis
Pulmonary nodule requiring evaluation
Excessive daily sputum production
Previous thoracotomy
Obvious pleural disease
Active or inducible coronary ischemia
Pulmonary hypertension
Depressed LVEF(< 45 %)
Obesity (BMI >32)
Unable/unwilling to participate in pulmonary rehabilitation
Systemic steroids ≥ 20mg prednisone/day

(Abbreviations: TLC, total lung capacity; RV, residual capacity; FEV_1, first second forced expiratory volume; DL_{CO}, diffusion capacity for carbon monoxide; LVEF, left ventricular ejection fraction; BMI, body mass index)

Adapted from:

Reference 18 DeCamp MM Jr, McKenna RJ Jr, Deschamps CC, Krasna MJ. Lung volume reduction surgery: technique, operative mortality and morbidity. Proc Am Thorac Soc.2008 May 1; 5(4):442-6.

Reference 24 DeCamp MM Jr, Lipson D, Krasna M. Minai OA, McKenna RJ Jr, Thomashow BM. The evaluation and preparation of the patient for lung volume reduction surgery. Proc Am Thorac Soc. 2008 May 1;5(4):427-31

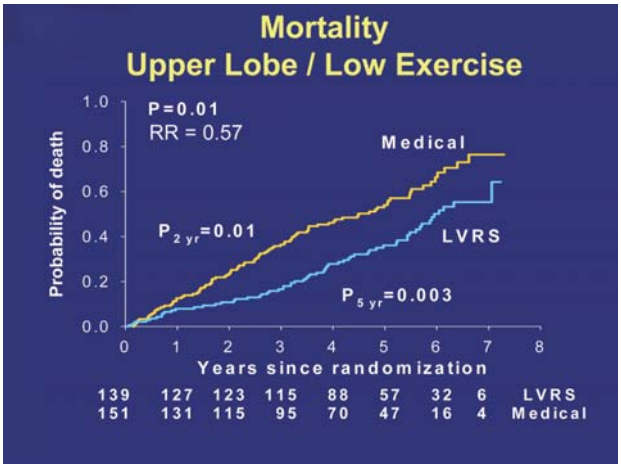

Fig. 2 Long-term mortality of the most favorable cohort of patients treated with LVRS versus maximal medical therapy in the National Emphysema Treatment Trial. These patients had an upper lobe predominant pattern of emphysema and low exercise capacity despite completing preoperative pulmonary rehabilitation. Note the highly statistically significant (p=.01) reduction in relative risk of death (RR=0.57) for the surgical cohort.[17]

vices has vastly simplified resection from Brantigan's era where the lung parenchyma was clamped, cut and over sewn. Both carbon dioxide[27] and neodymium: yttrium-aluminum garnet (Nd-YAG) lasers[28,29] have been used for LVRS. McKenna published the only prospective, randomized comparison of stapled resection versus laser ablation.[30] They demonstrated an 18% incidence of delayed pneumothorax and only a 13% mean improvement in FEV1 following laser therapy. Laser LVRS has been abandoned. Plication has been proposed as an alternative to LVRS with reported results similar to stapled resection.[31] This technique requires use of a non-cutting stapler and specialized instruments. As it is technically somewhat more demanding, it has not been widely practiced.

While Brantigan's initial approach to LVRS was unilateral via a posterolateral thoracotomy[6], Cooper's resurrection of the concept involved a bilateral approach accessing both lungs through a median sternotomy.[7,22] During this same era, video-assisted thoracoscopy (VATS) was becoming widely adopted for a variety of thoracic applications.[32] Unilateral LVRS via VATS appeared safe with a reported mortality of 2-3%, nearly a 2 week hospital length of stay (LOS) and a 27-35% improvement in FEV1 at 6 months post-procedure.[33-35] Soon others demonstrated that bilateral VATS was feasible with similar mortality and LOS.[11,36,37] The current standard of care is a bilateral, buttressed, stapled resection of approximately 80% of the right upper lobe and 60% of the left upper lobe (typically sparing the lingula).

A debate ensued as to the optimal surgical approach to bilateral LVRS. Published within a few months of each other, Cooper *et al*[22] and McKenna and colleagues[36]

each presented large clinical experiences (N ≥ 150) performing bilateral LVRS via median sternotomy or VATS respectively. In both series the operative mortality was 4% and the observed mean improvement in FEV1 at 6 months was 51-52%. Prior to NETT there was no randomized information regarding the optimal incisional approach. Secondary randomization within NETT (N=148; 77 Median sternotomy, 71 VATS) allowed for a prospective comparison of LVRS outcomes after median sternotomy or a bilateral VATS approach. There were no differences in operative mortality, survival, functional outcomes (FEV1, 6-minute walk distance) or quality of life measures between these two approaches. In general, patients undergoing bilateral VATS LVRS spent one less day in the intensive care unit, nearly 2 days less in hospital and were more likely to be living independently at 30 days postoperatively. The cost of hospitalization was on average $ 7000 less for patients undergoing VATS. The mean total healthcare-related costs for the 6 months after surgery were also $ 6500 less in the VATS group.[19]

Outcomes and Utilization

The National Emphysema Treatment Trial categorized patients into five groups based on preoperative assessment of functional capacity, physiologic tests, and imaging procedures. Among all 608 patients assigned to surgery, 90-day mortality was 7.9%. Exclusion of the 69 patients in the high-risk group (FEV_1 less than 20% predicted and either homogeneous CT distribution of emphysema or diffusing capacity less than 20% predicted) leaves 539 surgical patients who experienced a 90-day operative mortality of 5.2%.[14,17,19]

LVRS is an operation with significant morbidity. Virtually all patients experience air leak during their convalescence and in 50% of patients this persists for greater than one week.[38,39] The predictors of prolonged air leak are based on patient factors and include a lower DLco, the degree of pleural adhesions and the use of inhaled steroids. The incidence and duration of air leak were not affected by the surgical approach (sternotomy versus VATS) or the type of stapler or buttressing material used. A prolonged air leak was however predictive of perioperative pneumonia, return to the ICU, requirement for mechanical ventilation and LOS.[39] Significant cardiovascular complications befell about 20% of patients with supraventricular dysrhythmias leading the list.[21] Advancing age and declining pulmonary function were predictive of both major pulmonary and cardiovascular morbidity.

The initial NETT outcomes reported in 2003[14] confirmed the previous reported results from observational[36,38] and small randomized studies[40,41] that in properly selected cohorts, LVRS confers durable symptomatic, physiologic and survival benefits. Mature NETT follow-up reported in 2006[17] demonstrated a 14% risk reduction for death for all non-high-risk patients receiving LVRS as compared to those randomized to best medical therapy (Figure 1). The trial also identified two characteristics that classify patients into groups with differing benefits from lung volume reduction surgery: upper lobe distribution of emphysema and exercise capacity following pulmonary rehabilitation. Those patients with upper lobe predominant emphysema and low preoperative exercise capacity despite completion of pulmonary rehabilitation had nearly a 50% risk reduction for death after LVRS as compared to continued medical therapy (Figure 2). All upper lobe predominant patients were more likely to experience significant and durable improvements in health-related quality of life (HRQOL) and exercise capacity than were patients with a non–upper lobe–predominant pattern.

The clinical evidence from these cooperative trials appeared to support lung volume reduction as a sound physiologic approach to palliate dyspnea in patients suffering from emphysema. Following their analysis of NETT's results, Medicare issued a coverage decision to reimburse for LVRS in the non-high risk group of patients.[42] An experienced multidisciplinary team at Columbia has continued to offer LVRS post-NETT with no 90-day mortality and 98% 3-year actuarial survival.[43] Using a multidimensional predictor of outcome (BODE index) which includes spirometry, exercise tolerance and QOL; they found a $p < 0.0001$ likelihood of sustained improvement in BODE of greater than 2 points.[44] There is now convincing evidence through both observational and randomized studies that LVRS improves pulmonary function, exercise capacity, HRQOL and in one subset survival. On balance LVRS offers clear therapeutic benefits in a highly debilitating illness but, for unclear reasons, it is rarely performed and thus underutilized. Fewer than 200 LVRS operations per year have been performed on Medicare patients in the US since 2007.

Bronchoscopic Lung Volume Reduction (BLVR)

The reasons behind this surprising low utilization are not obvious but may be due to the prevailing errant impressions that LVRS is minimally effective with unacceptably high morbidity and mortality. The low utilization despite the evidence identified for entrepreneurs in the medical-device arena a sizeable "unmet clinical

need" and spurred a new wave of interest in non-operative approaches with the goal of achieving the benefits of LVRS without the perceived high morbidity, mortality and financial cost.

Three bronchoscopic lung volume reduction (BLVR) strategies (2 different unidirectional endobronchial valves and the creation and maintenance of extra-anatomic airway bypass tracts to relieve hyperinflation using drug eluting stents) have been developed and tested in pivotal randomized clinical trials in an attempt to meet this clinical need. The mortality and morbidity of BLVR is substantially lower than those of LVRS. The nature of morbidity depends upon the device used. None have received Food and Drug Administration (FDA) approval to treat emphysema in the US. Each of these BLVR procedures when analyzed in phase II trials showed that some clinical indices improve in the short term (3-12 months) but to a lesser magnitude than following LVRS. The mid-term (1 to 3 years) durability and complications of the various BLVR devices are not known. Most all devices resulted in improvement in QOL values above minimal clinically important difference (MCID) levels of 4 units on the St. George's Respiratory Questionnaire (SGRQ). This surpasses the mean change of 3.5 units in SGRQ reported from the large pharmaceutical trials with Salmeterol/Fluticasone (TORCH) and Tiotropium (UPLIFT)[45] but are far below the 8 SGRQ units (2X MCID) used to define NETT responders.[13,14,45] Exercise capacity following BLVR has shown little to no improvement regardless of the device/technique.

Endobronchial Valves

Two endobronchial valve devices have been or continue to be tested in clinical trials; EndoBronchial Valve (EBV) (Emphasys Medical Inc; Redwood City, CA) and Intrabronchial Valve (IBV) (Spiration Inc; Redmond, WA). The EBV device is a self-expanding nitinol stent with a silicone one-way duckbill valve which allows expiratory airflow but is closed during inspiration. It can be placed in the segmental or subsegmental airways with a flexible bronchoscope.[46] It was tested in the pivotal randomized VENT trial (N=321) with statistically significant but clinically irrelevant improvement in FEV1, 6-minute walk distance and respiratory specific QOL.[47] Optimal response was seen in cases of complete lobar exclusion (CLE). The EBV device has been approved for use in Europe but did not receive FDA approval and was sold to a competitor, Pulmonx Interventional Pulmonology; Redwood City, CA.

The IBV device is an umbrella-shaped device which is also self-expanding and available in different sizes to be placed, repositioned and/or removed with a fiberoptic bronchoscope.[48] In a 98 patient multicenter, nonrandomized, bilateral pilot experience a total of 659 valves (6.7 valves/patient) were deployed. There were no significant changes in spirometry and 6-minute walk distance at six-month or 12-month follow-up. However, quality of life as measured by the SGRQ improved by four or more units in 53% and 55% of the patients at 6 and 12 months, respectively.[49] Spiration completed but has yet to report on a double blind, multicenter randomized clinical trial on patients with upper lobe predominant disease. Controls received sham bronchoscopy. Primary efficacy endpoints were SGRQ and changes in lung volume as measured by computed tomography.

Extra-anatomic Airway Bypass

The creation of bronchial fenestrations was proposed by Lausberg and colleagues[50] for treating homogenous emphysema with the hypothesis that such non-anatomic connections between the hyperinflated pulmonary parenchyma and bronchial tree would decompress the lung, reduce its volume and thereby relieve dyspnea. The creation of such airway bypass tracts was intended for patients with significant hyperinflation and homogenous emphysema and is performed with a flexible fiberoptic bronchoscope in three steps using proprietary devices developed by Broncus Technologies Inc. (Mountain View, CA): 1. identification of blood vessels using a Doppler probe in the target territory of the segmental bronchi in order to avoid vascular puncture; 2. creation of the non-anatomic channel between the bronchus and hyperinflated air spaces with a needle-balloon catheter and; 3. deployment of a paclitaxel-eluting stent to dilate the fenestrated channel and maintain its patency. In a hyperinflated subset of Phase I/II trial patients, TLC, RV, FVC and SGRQ improved while 6-minute walk distance and FEV1 remained unchanged. Six months after airway bypass therapy, bronchoscopic follow up showed that 69% of stents remained patent.[51] The pivotal Exhale Airway Stents for Emphysema (EASE) trial randomized, using a 2:1 treatment to sham-bronchoscopy schema, 315 subjects in the US with homogeneous emphysema and an RV/TLC ratio ≥ 0.65. The primary endpoints were a 12% improvement in FVC and one or more point reduction in modified Medical Research Council's (mMRC) dyspnea scale. RV decreased by > 500ml in 40% of patients but only the mMRC endpoint was statistically significant while the FVC endpoint was not met.[52]

Table 2 Active Randomized Clinical Trials of Bronchoscopic Lung Volume Reduction

	FDA-Approved TRIALS		
	ASPIRE[53]	RENEW[54]	LIBERATE[55]
Device(s)	Aeriseal (foam)	LVR Coil	EBV, Chartis
Sample Size	300	315	183
Randomization Schema	3:2	1:1	2:1
Treatment	Bilateral	Bilateral-staged	Unilateral
Primary Endpoint	FEV1	6-minute walk	FEV1
Sponsor	Aeris Therapeutics	PneumRx	Pulmonx

New Technology

Three novel technologies are currently being investigated in FDA-approved pivotal trials. These ongoing investigations are summarized in Table 2. Aeris Therapeutics, Woburn MA is investigating the use of a foam sealant introduced with a flexible bronchoscope into bilateral upper lobe targets. Their ASPIRE trial[53] seeks to randomize 300 patients in a 3:2 schema of treatment versus best medical therapy. The primary endpoint is change from baseline in FEV1 at one year. PneumRx Inc, Mountain View CA is testing the placement of self-actuating nitinol coils bilaterally to mechanically compress hyperinflated regions in both heterogeneous and homogenous emphysema. They hope to randomize 315 patients (1:1 treatment versus best medical therapy) in their RENEW Trial[54] using change in six minute walk distance as the primary endpoint. Pulmonx is sponsoring the LIBERATE study[55] which proposes to use the EBV unilaterally in eligible patients who must have a heterogeneous pattern of emphysema and little or no collateral ventilation as assessed by their proprietary Chartis device. They will employ a 2:1 randomization schema of treatment versus best medical therapy with a goal of radiographic CLE. Their primary study endpoint is the number of treated patients with > 15% improvement in FEV1 at one year.

Considerable public (NIH and Medicare) and private industrial and entrepreneurial investment has been made in procedural and device-related therapies for emphysema. Analysis of the data generated by these efforts has led to a better understanding of the pathophysiology of the disease and the mechanisms which govern small airway obstruction, lung hyperinflation and the drivers of dyspnea. At present it appears unlikely that one specific approach to BLVR will address each phenotype of emphysema. Just as LVRS has been demonstrated to be safe and most beneficial in patients with upper lobe predominant disease, discreet BLVR interventions may prove best reserved for specific morphologies and/or severities. Responsible clinical practice warrants expanded referral for LVRS which has been proven safe, effective and durable for a subset of GOLD stage III/IV emphysema patients with focused evaluation of non-LVRS candidates for evolving BLVR strategies.

DISCLOSURE

All authors declare that this study has no conflict of interest.

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