Review Article

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Lung Volume Reduction in Chronic Obstructive Pulmonary Disease (COPD) – An Updated Review of Surgical and Endoscopic Procedures

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Abstract

The conventional medical management of emphysema using bronchodilators and anti-inflammatory agents has a limited benefit in patients having advanced hyperinflation of lungs due to destruction of elastic tissue. The natural course of COPD has been shown to be altered by only smoking cessation and oxygen therapy so far. The lung volume reduction surgery is viewed as another modality to change the natural history of emphysema in recent years. For patients with more generalized emphysema, resection of lung parenchyma improves elastic recoil and chest wall mechanics. An extensive literature search has demonstrated that carefully selected patients of emphysema (i.e. upper lobe predominant disease, low exercise capacity and FEV1 and DLco ≤ 20% of predicted) receive benefits in terms of symptomatic improvement and physiologic response following lung volume reduction surgery (LVRS). The resurgent interest in LVRS and National Emphysema Treatment Trial findings for emphysema have stimulated a range of innovative methods, to improve the outcome and reduce complications associated with current LVRS techniques. These novel approaches include surgical resection with compression/banding devices, endobronchial blockers, sealants, obstructing devices & valves and endobronchial bronchial bypass approaches. Experimental data and preliminary results are becoming available for some of these approaches. Most of the published studies so far have been uncontrolled and unblinded. Overall, extensive research in the near future will help to determine the potential clinical applicability of these new approaches to the treatment of emphysema symptoms.

Key words: *Lung volume reduction surgery, emphysema, endobronchial lung volume reduction*

Introduction

Chronic obstructive pulmonary disease (COPD) is a major and increasing global health problem that is predicted to become the third most common cause of death and the fifth most common cause of disability in the world by 2020 [1]. It is a systemic disease, with pulmonary side effects characterized by slowly progressive development of airflow limitation that is poorly reversible, in sharp contrast to asthma in which there is variable airflow obstruction that is usually reversible spontaneously or with treatment. The airflow limitation in COPD is usually progressive and associated with an abnormal inflam-

matory response of the lung to noxious particles and gases [2].

Cigarette smoking is the commonest cause of COPD (>90% of cases). The other risk factors implicated are air pollution (particularly indoor air pollution from burning fuels), genetic (α–1 anti-trypsin deficiency), airway hyper responsiveness and occupational exposure of irritants, etc. These factors initiate a chronic inflammation that leads to the destruction of alveolar macrophages, neutrophils and cytotoxic T lymphocytes as well as the release of multiple inflammatory mediators (lipids, chemokines, and cytokines). This is further amplified by a high level of oxidative stress due to free radicals from cigarette smoke. There is an imbalance [3,4] between activity of proteolytic enzymes (Neutrophil elastase, Proteinase 3, Metalloproteinase, Cathepsin G) and anti-protease (alpha-1 antitrypsin, alpha-1 chymotrypsin, secretary leukocyte protease inhibitors) resulting in elastolysis of alveolar walls by protease enzymes causing dilation of air spaces (static hyperinflation), loss of radial traction and elastic recoil. All these changes lead to loss of driving force during expiration, resulting in retarded early expiratory airflow, dynamic compression of bronchioles during expiration and development of internal positive end expiratory pressure (PEEP). The overall effect is an increase in lung volume (dynamic hyperinflation). Due to dynamic hyperinflation, the diaphragm becomes flat and is pushed down. Therefore, it generates less pressure during inspiration and the chest becomes barrel-shaped. Thus, there is a change in the shape of the rib cage, less apposition of diaphragm to the rib cage and altered orientation of muscle fibers, all these leading to a disparity between respiratory efforts and ventillatory output. This destruction and hyperinflation of the lung is patchy, which causes compression of a healthy lung, distortion of airways and a ventilation perfusion (V/Q) mismatch [3-5].

Management of COPD essentially includes smoking cessation, pharmacotherapy, prophylactic vaccination (against pneumococci and influenza), pulmonary rehabilitation, long-term oxygen therapy, etc. Bronchodilators are the mainstay of drug therapy for COPD and the most common agents used are inhaled anticholenergic and/or β-2 agonists and oral theophylline, etc. Corticosteroids are usually reserved for patients with severe COPD (Stage III & IV GOLD) or those with frequent exacerbations.

Despite medical therapy, significant numbers of patients with advanced COPD have a poor quality of life and are at an increased risk of death. These patients include those who have FEV_1 less than 45% of predicted value and those remaining symptomatic despite smoking cessation, optimum medical management, use of supplemental oxygen with rest or exertion and pulmonary rehabilitation. Management of such patients is difficult and possible treatment options left for these patients include LVRS or lung transplantation, depending upon the facilities and patient status [6].

Surgical management of emphysema has always evoked enthusiasm and numerous procedures have been proposed in the last century. Costochondrectomy, phrenic nerve interruption, thoracoplasty, glomectomy, radical hilar denervation, and pleural stripping are just a few of the procedures that have been tried. After an initial enthusiasm, all these procedures have found their respective places in the waste basket of history.

The concept of lung volume reduction for emphysema was proposed by a daring and innovative Brantigen et al. [7] as early as 1956. He advocated resection of the emphysematous portion of lungs, thereby improving V/Q mismatch of the remaining lung. A perioperative mortality of 18%, in the absence of objective measures to document objective benefit saw the fading away of the concept. With modern technology and more stringent patient selection, Cooper et al. [8] attained improvement in quality of life and a reduced operative mortality (4.8%). This helped in an enthusiastic and resurgent wave of LVRS with multiple trials subsequently.

Basis of LVRS

The National Emphysema Treatment Trials (NETT) was a multicenter, prospective, randomized controlled trial to examine the effects of optimal medical management and LVRS on short- and long-term survival, lung function, exercise performance and quality of life [9]. It showed that LVRS increases the quality of life, and confers symptomatic, physiologic and survival benefits. The exact mechanism by which LVRS confers these benefits is not well understood. The vari-

ous theories that are postulated are:

- Correction of elastic recoil by a reduction in volume of damaged lung segments, thereby allowing a resize of the remaining less-damaged tissues [10].
- The improvement of diaphragmatic curvature may result in an increase in length and contractility.
- A decrease in intrathoracic volume after LVRS may improve the left ventricular diastolic dysfunction.
- Reduction of dynamic air trapping by removal of emphysematous lungs that is associated with long expiratory time constants and a reduction in physiologic dead space, which in turn leads to increased exercise capacity [11]. Improvement in oxygenation, resulting in a decreased pulmonary vascular resistance and improvement in pulmonary hypertension.

Patient selection criteria for LVRS

Table 1 briefly summarizes the inclusion and exclusion criteria for patient selection for LVRS. These were adopted and modified by the NETT [12].

Apart from these specific criteria, patients with heterogeneous distribution of emphysema tend to experience greater improvement in postoperative FEV1 than those with homogeneous disease. Patients with an age <75 years, class III or IV dyspnoea and significant impairment in activities of daily living are also considered suitable for LVRS [13].

Methods of lung volume reduction (LVR)

Traditionally, the term LVRS is associated with sternotomy, and surgical resection of the emphysematous portion of the lung. Median sternotomy, the traditional approach, is now being replaced by Video-Assisted Thoracoscopic Surgery (VATS). After the NETT, newer investigations are centered on bronchoscopic endobronchial procedures and other less-invasive techniques to achieve LVR [14].

Currently, the new general conceptual approaches to LVR for which preliminary results have been published include surgical resection with compression / banding device, endobronchial volume reduction methods using a bronchoscope, i.e. endobronchial plugs, endobronchial valves, endobronchial sealants, endobronchial bronchial bypass approaches, endobronchial coils; and transpleural ventilation performed via minithoracotomy [15].

(I) Surgical resection with compression banding device

A variety of surgical approaches to LVRS have recently been reported. These include median sternotomy with bilateral stapling lung resection, VATS performed unilaterally or bilaterally with stapling lung resection, and unilateral VATS with Nd – Yag contact laser ablation of emphysematous tissue [6].

Conventionally, the patient is evaluated preoperatively for targeting worse areas of an emphysematous lung by using High Resolution Computed Tomography (HRCT) or quantitative lung perfusion scanning. A median sternotomy or VATS approach is then taken and a resection is done by an automatic stapling device followed by reinforcement patches using bovine pericardium strips, biologic fibrin glues, blood and Teflon reinforcement patches to prevent air leaks [16].

Table 1: Inclusion and exclusion criteria for LVRS.

Inclusion Criteria	Exclusion Criteria
• Emphysema refractory to medicalmanagement • Abstinence from tobacco for 3 months • Hyperinflation on Pulmonary Function Test (PFT) 1. Total Lung Capacity (TLC) > 110% 2. Residual volume > 220% of predicted value 3. FEV_1 < 45% of predicted value 4. FEV_1 increase < 30% or < 300 ml after bronchodilator administration • Predominant upper lobe disease on CT scan	• Continued smoking • Regular prednisolone >20 mg daily • TLC <20% • Giant Bullae > 5cm • Life expectancy < 2 years • PCO2 > 60 mm of Hg • Very severe impairments (FEV_1<0.4L) or disability (6-min walk <250 m), etc. • Serious systemic disease, unstable angina, coronary artery disease/poor cardiac functions, arrhythmias • Other significant lung diseases, such as infection, bronchiectasis, neoplasia, pulmonary hypertension, previous thoracotomy, extensive pleural disease

Recently, compression banding devices are used. The approach is the same, i.e. median sternotomy or VATS. The portion of the lung to be resected is drawn into a tube using suction. Then with the help of another tube, an elastomer sleeve is slipped over this portion of lung. The elastomer sleeve is fixed with the help of a suture. Then the lung and sleeve covering it is resected leaving a small band of compressive elastomer fixed in place. This decreases the incidence of air leaks [16].

Laser therapy for LVRS is applied either in direct contact with the lung surface or as a beam directed at the lung from a distance. McKenna et al. [17] compared laser bullectomy and LVRS and found no significant difference between both groups in mortality, hospital stay, and air leakage beyond seven days. Laser therapy was associated with a significantly increased rate of delayed pneumothorax and supplemental oxygen, while VATS was associated with comparatively reduced morbidity, less pain, earlier mobilization, a shorter hospital stay and a more rapid return to an exercise program [6].

Table 2 shows the subgroup analysis of the patients who underwent LVRS and their different outcomes [18,19].

(II) Bronchoscopic lung volume reduction

With the publications of the result of NETT, an increase in the number of patients undergoing LVRS was expected. However, the strict patient selection criteria and associated high morbidity of 58.7% were the likely reasons for the decrease in patients undergoing lung volume reduction surgery even after the publication of NETT data [20]. To reduce the costs, perioperative morbidity and mortality, bronchoscopic methods of lung volume surgery were proposed. Some of these procedures may be done as outpatient procedures also. These techniques are still in the trial phase and are not FDA-approved.

(A) LVR using bronchial plugs

This procedure is based on the theory that LVR could be accomplished by placing a device in a proximal airway to obstruct ventilation to the lung distal to obstruction. Gas that is trapped beyond the obstruction gets absorbed later, resulting in a sustained collapse of the lung, until the obstruction remains in place. Devices are placed under general anesthesia using a rigid bronchoscope into one or more segments of the lung. The devices used are silicone balloons, stainless steel stents containing biocompatible sponge, silicon plug, endoscopic Watanabe Spigot, etc. The reported complications include pneumonia, pneumothorax & paradoxical hyperinflation as well as the need for repeat endoscopic procedures [21].

(B) LVR using bronchial valves

A one-way endobronchial valve placed at segmental or lobar level blocks inspiration at that area but allows expiration and creates a lobar atelectasis. Two types of valve have been proposed for LVR. They are the duck bill endobronchial and umbrella-shaped intrabronchial valves. Both have the same working principal of preventing inspired air from entering the hyperinflated lung, while permitting the exit of mucus and gas during exhalation.

Emphasys is a self-expanding nitinol stent with a silicon one-way 'duck bill' valve. They were associated with improvement in FEV1, Forced Vital Capacity (FVC), Residual Volume (RV), and 6 Minute Walk Distance (6 MWD) without meeting minimal clinically important levels. Device malfunction, pneumonia distal to the valve, valve expectoration / migration, and

Table 2: Subgroup analysis of the patients undergoing LVRS and their different outcomes.

Subgroup	Disease extent	Exercise capacity	Long-term, short-term benefits of LVRS	Recommendation for LVRS
I	Bilateral upper lobe disease	Low	Decrease in long-term & short-term mortality	Beneficial
II	Bilateral upper lobe disease	High	No change in mortality, improved quality of life	Symptomatic benefit
III	Non-upper lobe predominant disease	Low	Increased 90-day mortality	Not recommended
IV	Non-upper lobe predominant disease	High	Increased short- and long-term mortality	Strong NO

granulation tissue on the prosthesis are major and significant complications [22].

Spiration, an intrabronchial valve, is an 'umbrella-shaped' self-expanding device, consisting of a polyurethane membrane on a nitinol frame. On bronchoscopic introduction, it is not associated with valve migration, erosion or hemoptysis. Removal of the prosthesis is justified for patients developing pneumonia, COPD exacerbation, pneumothorax and/or bronchospasm. Serendipity regarding endobronchial valves thus employed is the ability to reduce persistent pulmonary leaks, and results in reduction or resolution of pneumothorax in > 90 % of cases [23].

VENT (Endobronchial Valve for Emphysema Palliation Trial) was the first prospective randomized multicenter controlled trial to evaluate bronchoscopic LVR, compared to medical care in severe heterogenous emphysema [14]. This showed improvement in FEV1 and 6-minute walk distance, compared to controls, but the pneumonia, haemoptysis and acute exacerbation of COPD requiring hospitalization were more after the endobronchial valve.

(C) LVR using endobronchial airway sealants (Bio LVR)

In this approach, LVR is achieved by using a tissue engineering procedure in which a series of biologically active reagents (Chondroitin sulfate, polylysine in fibrin glue and thrombin solution) are delivered through a flexible bronchoscope to promote scar formation in the diseased areas of a lung, leading to the replacement of emphysematous lung tissue by a contracted organized scar. This approach is less affected by the presence of collateral ventilation, but the effects of the treatment are irreversible. The advantages of this technique are that it is minimally invasive, incremental application is possible, air leaks are minimal and the procedure can be performed on an outpatient basis. Disadvantages include the risk of infection and the technique must ensure that occluded segments will not spontaneously reopen despite collateral circulation over time [21,24].

The complications are minimal and similar to any induced inflammatory response that subsides after 24 to 48 hours. Bronchoscopic injection of autologous blood and fibrinogen into an emphysematous bulla has also effected similar volume reduction [25].

(D) LVR using bronchial fenestration and airway bypass

In patients with emphysema, there is an increase in dynamic expiratory resistance in small airways with an associated increase in collateral ventilation due to the early collapse of airways during expiration. In order to bypass the high resistance, direct connection between the bronchus and collaterally ventilated lung parenchyma is made using non-collapsible, paclitaxel eluting bronchial stents, thereby creating a new conducting expiratory airway. This procedure is a bronchus airway bypass procedure that creates a parallel shunt pathway from damaged lung parenchyma to the central airways using a radio frequency ablation catheter [26]. By bypassing the small, floppy, collapsing airways in the damaged area of the lung, these shunt pathways lower the regional closing volume, resulting in more effective emptying. This approach alters the dynamic component of gas trapping that results from a premature airway closer leading to improved expiratory airflow and decreases resistance. This approach is being proposed for patients with more homogenously distributed disease, who are currently considered to be poor candidates for LVRS [16].

Although an innovative and physiologically sound approach, it has certain limitations, including risk of bleeding, complexity of the procedure, specialized training & equipment and the tendency of radio frequency ablation shunt pathways to close, thereby limiting long-term effectiveness of this procedure [21]. The Exhale Airway Stent for Emphysema (EASE) trial evaluated the airway bypass method in 208 patients with severe homogenous emphysema. The technique was safe with transient improvement but benefits were not sustainable [27].

(E) Bronchoscopic thermal vapor ablation

Controlled doses of thermal power can produce an inflammatory response that results in targeted, complete and permanent lung volume reduction. This method requires a reusable vapor generator with a disposable bronchoscopic catheter to deliver heated water vapor to target regions of the emphysematous lung via a bronchoscope. This procedure has an advantage that it requires no insertion of prosthesis and is not affected by collateral ventilation. There has been no documen-

tation on the benefits of spirometry, but St. George's Respiratory Questionnaire showed improvement. Side effects noted include COPD exacerbations and pneumonitis. This is still in the trial phase [28].

(F) Endobronchial lung volume reduction coil

Self-activating coils placed into the airways through a bronchoscope are another method to achieve LVR. LVR coils (PneumRx) are placed bronchoscopically into the most diseased regions in severe emphysema patients using a proprietary delivery system to achieve lung tissue compression. Complications include cough, dyspnoea, COPD exacerbation and chest pain, etc. The procedure requires multiple attempts and multiple coil placement [29].

Table 3 summarizes the various bronchoscopic techniques and their comparison to achieve LVR.

(G) Other methods - Transpleural ventilation

In this technique, modified chest tubes are placed externally into the most emphysematous lung tissue to enhance external deflation via mini thoractomy. The procedure is reversible and not affected by collateral ventilation. This approach has been shown to improve FEV1, 6MWD, dyspnoea score values and reduce RV & Total Lung Capacity (TLC) in a limited number of trial patients [30].

Benefits of LVRS

Strictly selected groups of patients undergoing LVRS have long-term functional improvement in exercise tolerance and an improved quality of life and less mortality [31]. In a study involving 16 patients with severe emphysema, LVRS also resulted in improved sleep quality and nocturnal oxygenation. Improvement in nocturnal oxygenation correlated with improved airflow, and a decrease in hyperinflation and air trapping [32].

In a study of 98 patients, those treated unilaterally showed a trend toward greater improvement than those treated bilaterally. A similar trend toward improvement was also observed in patients who had one entire lobe treated, compared to those with just one or two bronchopulmonary segments treated [33].

The NETT has reported the initial study findings, demonstrating survival and functional benefits in subgroups of patients undergoing LVRS. This has been observed in patients with both predominantly upper lobe

Table 3: Comparison of various bronchoscopic lung volume reduction procedures

S. No	Technique	Mechanism	Results	Repeatability	Effect on collateral ventilation	Complications
1.	Endobronchial valves	Cause segmental / Lobar atelectasis by blocking inspiration but allowing expiration	Improvement in FEV_1, 6MWD, BODE index, etc.	Yes	Yes	Pneumonia, valve dysfunction, hemoptysis, COPD exacerbations.
2.	Endobronchial sealants (BioLVR)	Biological agent instilled regionally to produce scarring and collapse of emphysematous areas.	Improved lung functions for up to 6 months	No	No	Pneumonia
3.	Thermal vapor ablation	Heated water vapours delivered to target emphysematous lobar segments to promote injury and fibrosis.	Improvement in St.George Resp. questionnaire.	No	No	Hemoptysis, COPD exacerbation, pneumonia, atrial tachycardia.
4.	Bronchial fenestration & airway bypass	Extra anatomic passage way created through walls of the natural airways to connect damaged lung parenchyma and the naïve airways, thereby enhancing deflation by "bypass mechanisms".	Improvement in FVC and dyspnoea score.	Yes	No	Hemoptysis
5.	Endobronchial coils	Implantation of coils to achieve parenchymal compression.	Substantial improvement in pulmonary function, lung volumes, 6 MWD, and quality of life.	Yes	No	Cough, dyspnoea, chest pain.

emphysema and low baseline exercise capacity [18]. In another study, the postoperative BODE index (Body Mass Index, Degree of Airflow Obstruction Assessed by Spirometry, Grade of Dyspnoea and Exercise Capacity) was found to be a powerful predictor of survival in COPD patients after LVRS [34]. The cardiac subset of NETT assessed the effect of LVRS on resting pulmonary hemodynamic in 55 patients and data confirmed that LVRS does not raise pulmonary arterial pressure by a decrease in intrathoracic pressure [35].

Limitations of LVRS

Much of the controversy surrounding LVRS involves the variability of response among patients, limitation in the magnitude of the response, cost and concerns about the duration of improvement [36-38]. Air leak remains the major morbidity following LVRS [39]. The complications associated with bronchoscopic Lung Volume Reduction have already been mentioned.

The LVRS is also not without risk [21]. Of the 511 patients of the non-high-risk group in NETT, the incidence of operative mortality was 5.5%, major pulmonary morbidity 29.8% and cardiovascular morbidity 20%. There is an increased mortality pattern, particularly in patients with FEV1 < 20% predicted, homogenous emphysema on HRCT or emphysema predominantly in lower lobes or carbon monoxide transfer <20% [40]. Finally, LVRS is costly relative to medical therapy in the short term. However, it may be cost-effective if benefits could be maintained over a long period [41].

In conclusion, resectional LVR has been found to be superior to medical management in reducing dyspnoea and improving lung functions, survival and quality of life in a very selected, low-risk group of patients with predominant upper lobe heterogenous emphysema. However, this approach of management is associated with increased risk of pulmonary and cardiac morbidity and even mortality as a result of surgical intervention. To overcome the demerits of LVRS, a number of innovative, non-surgical approaches for achieving LVR in advanced emphysema are currently being developed and evaluated in clinical trials. Extensive research in the near future on some of these less-invasive and non-resectional lung volume treatments by bronchoscopic methods will help to determine the potential clinical applicability of these new approaches, to reduce the medical and financial burden associated with treating patients with advanced emphysema, including the homogenous variant [42].

Conflict of interest statement

The authors do not declare any conflict of interest or financial support in this study.

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