

Review Article

Advances and applications of bronchoscopic lung volume reduction

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Abstract: Lung volume reduction surgery usually gives rise to high postoperative morbidity and impedes its further application. Recently, a plethora of bronchoscopic lung volume reduction techniques such as one-way endobronchial valves, biological sealants, thermal vapor ablation, airway bypass stents and lung volume reduction coils have been extensively used in emphysema treatment. The current data for bronchoscopic lung volume reduction although not conclusive enough do present multiple safer ways compared with conventional surgery with few serious complications, lower cost and shortened hospital care. The bronchoscopic lung volume reduction will undergo continuous development as constant randomized trials are performed to prove its full efficacy.

Keywords: Bronchoscopic lung volume reduction, lung volume reduction surgery, emphysema, safety

Introduction

Emphysema is a progressive disease with symptoms of characteristic cough and shortness of breath. It usually happens among smokers and may pose serious threat to individuals. Patients with heterogeneous emphysema and a low baseline exercise capacity have been identified as a subgroup within Chronic Obstructive Pulmonary Disease (COPD) [1]. People with severe emphysema who have quit smoking usually suffer a lot from irreversible airway obstruction even after canonical medical treatment. Moreover, loss of recoil can also cause expiratory air flow limitations and further deteriorate the health state. Air trapping induced by exercise can reduce inspiratory capacity and this restriction in capacity and only be compensated by increasing respiratory rate therefore resulting in a vicious cycle of air trapping.

Lung volume reduction attempts to remedy the loss of elastic recoil by largely removing the most damaged lung segments and allowing the remaining tissues to reshape. By eliminating parts of potentially 'dead' lung tissues, the air trapping can be partly released and exercise capacity can be further elevated.

Therefore, lung volume reduction can improve the quality of life among patients with severe emphysema.

A recent study from National Emphysema Treatment Trial (NETT) argues that patients with upper lobe emphysema can benefit from lung volume reduction surgery by comparing traditional medical treatment with combined LVRS therapy [2, 3]. However, canonical lung volume reduction has increased short-term mortality around 5% and serious postoperative morbidity (~58.7%). The cases are further complicated with increased risks of arrhythmias (24%), respiratory failure (22%), pneumonia (18%) and myocardial infarction (1%). About 28% patients were hospitalized for as long as 1 month after surgery. Only 30% patients derived a clinically significant improvement as reported. Therefore, the relatively high morbidity has posed serious problems to surgical lung volume reduction since the publication of NETT data. These factors have been the incentive for developing less invasive endoscopic modalities. In a more recent NETT study, a generic quality of life (QoL) measure, known as the Quality of Well-being (QWB) Scale, was evaluated. The QWB scores before death for patients in the LVRS group improved up to the Year 2 visit, while scores for

the Medical group dropped significantly following the baseline visit. In comparison to maximal medical therapy alone, patients undergoing maximal medical therapy plus LVRS experienced improved health related quality of life and gained more quality-adjusted life years [4]. Therefore, bronchoscopic lung volume reduction (BLVR) has shed new lights on surgical treatment for patients with emphysema by using a range of modalities such as stents, valves, thermal vapor ablation, sealants and implants [5]. These new modalities may differ among each other and more importantly bring about huge advances compared with conventional lung volume reduction surgery. For example, airway bypass stents and valves have been applied in homogenous and heterogeneous emphysema respectively while homogeneous and heterogeneous emphysema can both be relieved by biological sealants. Here we review recent modalities in surgical emphysema treatment with far less risk of complications.

One-way endobronchial valves

Endobronchial Valves (EBVs) is among the most intensively investigated techniques. By valve insertion into the bronchial lumen, valves may allow one-way flow of secretions and air out of an occluded pulmonary segment during expiration but prevent any distal flow during inspiration. Currently, 2 distinct endobronchial valves are widely studied: duckbill (Zephyr from Pulmonx, Inc.) and umbrella-shaped valves (IBV from Spiration, Inc.). Domestic valves are also intensively investigated but only applied in animal experiments.

Earlier reports on duckbill valves-Zephyr are mostly non-controlled studies [6-8]. In 2010, a great multicenter trial (Endobronchial Valve for Emphysema Palliation Trial) using large samples has provided crucial insights into the efficacy of endobronchial valves [9]. Totally 321 patients were enrolled and were treated with Zephyr EBV (i.e. treatment group) and medical surgery (i.e. control group) according to a 2:1 ratio. In a 6 to 12 month follow-up study, the subgroups with EBV has increased forced expiratory volume in 1 second (FEV_1) by 6.8% (60 ml), and 6-minute walking test (6 MWT) by 5.8% (19 m). Endobronchial-valve treatment for advanced heterogeneous emphysema induced modest improvements in lung function, exercise tolerance, and symptoms at the

cost of more frequent exacerbations of COPD, pneumonia, and hemoptysis [10, 11]. In recent Euro-VENT study, it was reported that patients with intact fissurae interlobaris and complete block can improve FEV_1 by 26% and reduce targeted lung volume by $80 \pm 30\%$ [10]. The trial also demonstrated a strong necessity for complete block while the heterogeneity in emphysema tissues may play secondary roles. Meanwhile, a follow-up study after 12 months also suggested a clinical efficacy. Recently, Patrick et al. showed that the noninvasive ventilation given to patients with acute hypercapnic exacerbation of chronic obstructive pulmonary disease significantly reduces mortality and morbidity. Furthermore, lung volume reduction surgery is effective in patients with heterogeneous upper zone emphysema and reduced exercise tolerance, and is probably underused using duckbill valves-Zephyr [12]. EBV can fully block pulmonary lobe at specific sites to impede flow into distal airway from proximity. In June 2011, a Dutch prospective randomized control trial (STELVIO trial, NTR2876) investigated the efficacy of Zephyr treatment in patients with high heterogeneity but with no collateral flow. This trial is expected to be completed by 2014 [13].

Collateral ventilation (CV) has been put forward by Van Allen as early as 1931 [14]. In normal individuals, there exist multiple structures such as Kohn's alveolar pores, bronchiolar channels of Lambert and inter-bronchiolar pathways of Martin [14-16]. However, under normal conditions, collateral ventilation is shut down owing to overwhelming bronchiolar airway resistance. However, in patients with emphysema, the collateral ventilation is upregulated by 10 fold compared with healthy individuals because of impaired pulmonary infrastructure and reduced bronchiolar resistance [17]. Chartis Pulmonary Assessment System can be used to quantify collateral ventilation. Significant reduction in lung volume (> 350 ml) can be achieved in patients with CV- (assessed by Chartis system). In Herth et al.'s study, 80 EBV patients underwent a pre-treatment Chartis assessment. Before and 30 days after implantation, high-resolution computed tomography scans were taken (with a cut-off ≥ 350 mL) [18]. Of the 51 patients classified as having an absence of CV according to their Chartis reading, 36 showed a TLVR ≥ 350 mL. Chartis showed an accuracy level of 75% in predicting whether or not the

target lobe volume reduction (TLVR) cut-off would be reached [18]. In CT imaging, intact fissurae interlobaris may guarantee no CV. Another *in vitro* study by Higuchi et al. suggested that CV is correlated with the homogeneity of emphysema but not with intact fissurae interlobaris [19]. Further study is needed to clarify the underlying mechanisms associated with CV.

Umbrella-shaped valves are less investigated. IBV may not block all unilateral lobes but instead be placed upon double upper lobe. Recent study covering 36 enrolled patients with IBV treatment suggested a non-significant improvement in pulmonary function, Dyspnea index and quality of life [20]. This study implies that partial block in pulmonary lobes with IBV is ineffective [21]. Following the first pilot studies on small number of patients documenting the safety and the feasibility of the procedures, few multicenter trials have been performed with either device showing some beneficial effects lasting for up to 12 months in selected patients [22].

Taken together, EBV can achieve significant lung volume reduction for patients with heterogeneous emphysema, intact fissurae interlobaris and non-collateral ventilation [23]. The improvement in FEV_1 with EBV treatment is comparable to that with LVRS [24]. However, EBV is superior to regular LVRS owing to elevated safety. The only reported mortality was aroused by combined pneumonitis after EBV implant [6]. Canonical complications include severe COPD (5%~20%), pneumothorax (7%~11%) [6, 7, 25, 26]. It was reported that pneumothorax is positively correlated with atelectasis [27]. However, the status of the heterogeneity in emphysema and collateral ventilation may not determine the efficiency of EBV treatment. One report suggested that patients with $\alpha 1$ -antitrypsin deficiency can also benefit from EBV treatment implying that EBV can be used in patients with late emphysema prior to pulmonary transplantation [28, 29].

Biologic lung volume reduction

Biological agents aim to reduce lung volume by sealing off the most emphysematous areas [30, 31]. The rapidly polymerizing sealant is designed to work at the alveolar level. The mechanism involves atelectasis resorption

from airway occlusion and subsequent remodeling. This remodeling will lead to scarring-induced contraction of lung parenchyma, and functional lung volume reduction can be expected one to two months. Recent pathological analysis using sectioned pulmonary tissues from patients taking lung volume reduction by biological sealants suggested that nearly all pulmonary tissues exhibited non-necrotizing granulomatous inflammation containing epithelioid cell granulomas and Langerhan's type giant cells indicative of a foreign body reaction with no signs of necrosis, fibrosis and hyperplasia [32]. This characteristic inflammatory response suggested a repair at alveolar level. Biological sealants can therefore reduce pulmonary volume and block CV. Kramer et al. found that biological sealants can effectively reduce lung volume at both lobes (895 ± 484 mL, $P < 0.001$) with improved FEV_1 ($25.0 \pm 3.3\%$) 1 year post surgery. At 2 year post surgery, the FEV_1 was further increased ($14.3 \pm 33.1\%$). Meanwhile, FVC and CO dispersion were also increased by $5.8 \pm 23.2\%$ and $10.6 \pm 20.6\%$, respectively [33]. Another study from 25 heterogeneous emphysema patients suggested that those at GOLD III stage can benefit more with biological sealants compared with IV stage, such as improved pulmonary function, 6MWD, mMRC and SGRO [34]. Magnussen et al. further showed that in contrast to EBV, treatment with biological sealants is uncorrelated with the integrity of fissurae interlobaris [35]. In all, treatment with biological sealants is demonstrated to be a safe strategy. Although the efficacy is associated with the dosage of sealing agents, the long-term effect demands further investigation.

Thermal vapor ablation

Controlled doses of steam, when delivered to a segmental airway, can produce massive inflammatory responses resulting in lung volume reduction. Similar to biological sealants, the treatment with thermal vapor ablation is not affected by CV [36]. A 2mm vapor catheter is inserted via bronchoscopy to targeted airways. On the vapor catheter, there is a distal occlusion ball which functions as an isolator among lung segments. Recently, Snell et al. conducted a research enrolling 42 patients with unilateral heterogeneous emphysema at upper lobe [37]. In a 6-month follow-up study, the authors found that FEV_1 was elevated by

141 ml (17%) and the residual was reduced by 406 ml. Meanwhile, there was a 48% reduction at pulmonary volume. SGRO score was also improved by 14%. 6MWT and mMRC were both elevated by 46.5 m and 0.9 points, respectively. Canonical complications contained severe COPD, pulmonitis and hemoptysis. Local inflammatory responses culminated at 2~4 weeks post surgery. Meanwhile, the study also showed that patients with significantly higher inflammatory responses can achieve better clinical prognosis [38]. Another report by Gompelmann et al. also demonstrated that thermal vapor ablation is an effective way to lung volume reduction and is not correlated with the integrity of fissurae interlobaris [39].

Airway bypass stents

Airway bypass aims to create an extra-anatomic bronchial fenestration to deflate emphysematous lung parenchyma. This technique may depend on the presence of collateral ventilation where alveoli ventilation that bypass the airways [13, 40]. This treatment was always used to combat homogeneous emphysema. Current procedures about airway bypass contain 3 steps. Selection of an area of segmental bronchi free of blood vessels using Doppler probes, fenestration of the airways and locating a paclitaxel eluting stent to prevent granulation induced obstruction to the stent [41]. Recent data on 35 patients with homogenous emphysema who had bypass stents placed in both lungs showed that using airway bypass stent can improve the prognosis among RV/TLC patients larger than 67% but less effective for other patients. The EASE trial in 2011 which involved 208 patients assessed the effect of airway bypass stent [42]. Also patients underwent effective recovery and were assigned to treatment (i.e. with airway bypass stent) and control group at 2:1 ratio. 6MWT and mMRC score did not improve significantly evaluated at 1, 3, 6 and 12 month. However, in a 6-month follow up, the stents were lost in most cases by CT scans possibly owing to chronic cough and expectoration. There was significant granulation in remaining stents and obstruction in bypass.

Lung volume reduction coils

Lung volume reduction nitinol coils with flexible sizes can be inserted into target lumens of

bronchia under fluoroscopic guidance. The released coils can reshape themselves and bend multiple bronchia to reduce lung volume [43, 44]. The airway implants do not depend on the presence of CV. Lung volume reduction coils have not been investigated intensively. One preliminary study involving 11 patients suggested that the insertion of nitinol coils do not lead to detrimental effect such as pneumothorax [45]. The study also demonstrated a positive therapeutic effect to heterogeneous emphysema. Another study by Slebos et al. who enrolled 16 heterogeneous patients showed that the adverse effects usually take place at 30 days post surgery with insertion of 28 coils [46]. These side effects include slight hemoptysis, short-term thoracalgia and acute COPD. A follow-up study for 6 months demonstrated an improvement in SGRQ score by 14.9%. FEV₁ and FVC were also increased by 14.9% and 13.4% respectively. The residuals were reduced by 11.4% while 6MWT was raised to 84.4 m. In a recently multicenter trial, Safety was evaluated by recording all adverse events, efficacy by the St George's Respiratory Questionnaire (SGRQ) as primary endpoint, and pulmonary function testing, modified Medical Research Council dyspnoea score (mMRC) and 6-min walk distance (6MWD) up to 12 months after the final treatment. Sixty patients (60.9 ± 7.5 years, forced expiratory volume in 1 s (FEV₁) 30.2 ± 6.3% pred) were bronchoscopically treated with coils (55 bilateral, 5 unilateral). LVR coil treatment results in significant clinical improvements in patients with severe emphysema, leading to a good safety profile and sustained results for up to 1 year [47]. Taken together although massive randomized trials are still needed, insertion of the lung volume reduction coil is indeed a promising way to effective emphysema therapy.

Conclusion

Bronchoscopic lung volume reduction appears to be safer than surgery and the enhanced safety provides an attractive way to severe COPD patients who are physiologically fragile. It is hoped that larger randomized trials can be performed in future studies. Although BLVR was under extensive experimental validation, the current data can more or less shed lights on combinatorial use of different modalities under complex emphysema situations with low risk of complications.

Disclosure of conflict of interest

None.

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