Evidence-based review of bronchoscopic lung volume reduction

Abstract

Emphysema sequentially leads to the loss of gas exchanging surface and an abnormal shape of the diaphragm generating dyspnea refractory to standard medical therapy. Lung volume reduction surgery (LVRS) is a surgical treatment option for patients with severe emphysema whose symptoms are uncontrolled on standard therapy. Bronchoscopic LVR (bLVR) is a process by which lung volume reduction is achieved in a minimally invasive manner using bronchoscopy-guided insertion of valves, coils, sealants, or by thermal vapour ablation like techniques. These therapies have developed over the last few years and have variable results in patients. We have summarized the current evidence available on each of these methods in this review.

Key words: bronchoscopy, pulmonary emphysema, treatment outcome

Introduction

Emphysema is a form of chronic obstructive pulmonary disease (COPD) defined by the abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles. Emphysema is associated with destruction of the alveolar walls leading to loss of elastic recoil, early airway closure during exhalation, and air trapping in the distal air spaces. These changes cumulatively lead to a loss of gas exchanging surface and an abnormal shape of the diaphragm.

Lung volume reduction surgery (LVRS) is a surgical treatment in advanced emphysema where dyspnea is uncontrolled on standard therapies. Bronchoscopic Lung Volume Reduction (bLVR) is an advanced bronchoscopic technique to treat hyperinflation due to emphysema [1].

The endoscopic techniques use one-way valves, coils, and sealants, as well as thermal ablation which result in the collapse of overinflated lung segments and achieve benefits similar to that of surgery [1].

Valves

One-way valves allow air and mucus to exit the treated area but do not allow air to re-enter, thus causing atelectasis of the hyperinflated segments distal to the valve. Two types of valves have been designed for this purpose. There is an endobronchial valve, known as the Zephyr valve (duck bill shaped), and an umbrella shaped intrabronchial Spiration valve [2]. The Zephyr valves are self-expanding valves made of nitinol with a silicone coating along with a unidirectional Hemilich valve. The intrabronchial valve has a similar mechanism of action. Its umbrella shape compresses against the airway acting as the valve. They are designed in such a way that they can be inserted bronchoscopically into the desired segment or subsegment and are available in different sizes to fit the airway properly so as to cause complete lobar occlusion. The VENT trial was an international, multicenter (USA and Europe), randomized control trial (RCT) to assess the efficacy and safety of endobronchial valve treatment in pa-
tients with heterogeneous emphysema (Table 1). The main inclusion criteria were COPD with a predicted forced expiratory volume in one-second (FEV$_1$) of 15–45%, predicted residual volume (RV) of > 150%, and heterogeneous emphysema on a chest computed tomography (CT) scan. The trial reported significant improvement in FEV$_1$, St. George’s Respiratory Questionnaire (SGRQ) scores, and six-minute walking distance (6MWD). Notable findings included increased heterogeneity, increased benefit, and a more clinically significant benefit of fissure integrity [3, 4]. The results of the VENT trial gave the insight that the absence of collateral ventilation (CV) between the treated lobe and the adjacent lobe is important. The finding led to the development of the Chartis system to measure functional collateral ventilation.

The STELVIO trial had 68 patients randomized to valve treatment vs standard care. This trial had used the Chartis system and also allowed for re-bronchoscopy to adjust the initial valve placement in case of a lack of target volume reduction. Endobronchial valve treatment demonstrated a +20.9% improvement in FEV1 for the treatment group vs +3.1% for the controls, an improvement in 6MWD of +60 m for the treatment group vs -14 m for the controls, and a SGRQ score difference of -14.7 points in favour of the treated patients (all p < 0.001) [5]. Post hoc analysis of these trials using quantitative CT (QCT) analysis also showed significant results for pulmonary func-

| Table 1. The summary of clinical trials in valve therapy |
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| Trial | Patient | Intervention | Duration of study | Comparison | Outcome | Adverse effects |
| VENT [3, 4] | Heterogeneous emphysema | EBV | 6 months and 12 months | Usual care | Mean between-group difference of 6.8% in the FEV$_1$ (p = 0.005) at 6 months | Complications composite EBV group vs Control group (10.3% vs 4.6%; p = 0.17) Rate of exacerbation of COPD requiring hospitalization (7.9% vs 1.1%, p = 0.03) Hemoptysis (6.1% vs 0%, p = 0.01) Pneumonia in the EBV group — 4.2% |
| STELVIO [5] | Severe emphysema and a confirmed absence of collateral ventilation | EBV | 6 months | Usual care | Mean between-group difference of FEV$_1$ = 140 mL (95% CI 55 to 225) FVC = 47 mL (95% CI, 107 to 588) 6MWD = 74 m (95%CI, 47 to 100) (p < 0.01 for all comparisons) | Serious adverse events EBV vs control group, (23 vs 5; p < 0.001) Pneumothorax (18%) Events requiring valve replacement (12%) or removal (15%) |
| IMPACT [7] | Homogeneous emphysema with absence of collateral ventilation assessed with the Chartis system | EBV | 3 months | Usual care | Mean between-group difference FEV$_1$, 17 % (p = 0.0002) | Procedure-related pneumothoraces occurred in 11 subjects (25.6%) |
| TRANSFORM [8] | Homogeneous emphysema with absence of collateral ventilation assessed with the Chartis system | EBV | 3 months and 6 months | Usual care | FEV$_1$ improvement of 12% or more 55.4% EBV vs control (55.4% vs 6.5%; p < 0.001) EBV subjects (89.8%) — target lobe volume reduction ≥ 350 mL, mean 1.09 ± 0.62 L (p < 0.001) Pneumothorax was the most common adverse event, occurring in 19 of 65 (29.2%) of EBV subjects |

6MWD — 6 minute walk distance; COPD — chronic obstructive pulmonary disease; EBV — endobronchial valve; FEV$_1$ — forced expiratory volume in one-second; FVC — forced vital capacity; SGRQ — St. George’s Respiratory Questionnaire
tion, exercise, and quality of life in patients with a homogeneous emphysema distribution [5, 6].

Consequently, there was a prospective, multicenter RCT called the IMPACT trial where endobronchial valve treatment was evaluated in patients (n = 93) with homogeneous emphysema in the absence of collateral ventilation (using Chartis). At 3 months after treatment, FEV1 improved by +13.7% from baseline in the valve treatment group vs -3.2% in the controls, 6MWD improved to 22.6 m vs -17 m, and quality of life measured by the SGRQ score improved by -8.6 vs +1.0 points (all p < 0.001) [7].

The encouraging results of the above trial lead to a multicenter trial in patients with heterogeneous emphysema and absent collateral ventilation (TRANSFORM trial). The trial showed that FEV1, improved +20.7% in the treatment group vs -8.6% for controls with a between-group difference in residual volume (RV) of 700 mL, 6MWD of 78.7 m, and SGRQ score of 6.5 points (all p < 0.001) [8].

The REACH trial, which focused on the adapted intrabronchial valve, demonstrated significant target lobar volume reduction on CT with a mean reduction of 779 mL. Also, at 6 months, the mean FEV1 improved to +12.9% for the treatment group vs -1.7% for controls (p < 0.001), and the SGRQ score improved to -9.1 vs +3.5 points (p = 0.0023) [9].

All the above trials using either endobronchial or intrabronchial valves have reported complications of pneumothorax, pneumonia, and exacerbation of COPD.

The Cochrane review of five studies using endobronchial valve treatment has shown significant improvements in FEV1 (standardized mean difference (SMD) 0.48, 95% CI 0.32 to 0.64) and in scores on the SGRQ (-7.29 units, 95% CI -11.12 units to -3.45 units). There were no significant differences in mortality between the two groups (OR 1.07, 95% CI 0.47 to 2.43) but adverse events were more common in the endobronchial valve group (OR 5.85, 95% CI 2.16 to 15.84) [10]. The quality of evidence ranged from low to high [10].

Studies have since been conducted to identify the best method to detect CV. CT-based analysis has been compared with the Chartis system with equivocal results, hence a combination of both these methods is best to achieve the best prediction with regards to CV [11, 12]. The ideal way to assess CV will hopefully come about along with improvement in technology in the near future. It is important to note that the use of valves has its own complications, most common of which are COPD exacerbation (9.3–64%) [3, 13], pneumothorax (4.2–25.6%) [3, 7], and pneumonia (3.2–11.7%) [3, 6]. These complications arise due to the insertion of the valve. This causes a constitutional change in the lobe of the lung leading to its collapse resulting in pneumothorax, with pneumonia causing further exacerbation. Selecting the right patient in terms of CV, ability to handle these complications, and a physician trained in handling these complications is important for the success of valve therapy.

**Coils**

The coils are nitinol devices delivered bronchoscopically using a unique delivery system into subsegmental airways. The first (1:1 RCT using coils (RESET trial) included patients (n = 45) with both homogeneous and heterogeneous severe emphysema, and these patients were treated bilaterally (Table 2). In this trial, the FEV1 improved by +10.6%, RV by -0.31 L, and 6MWD by +64 m, with a mean SGRQ score showing an improvement of -8.4 points when compared with the control group [11]. Afterward, two large randomized controlled trials (REVOLENS and RENEW) observed significant benefit in clinically important parameters [12, 13].

The Cochrane systematic review of the three studies comprising 461 patients showed that treatment with endobronchial coils had a significant between-group mean difference in FEV1, (10.88%, 95% CI 5.20% to 16.55%) and SGRQ score (-9.14 units, 95% CI -11.59 units to -6.70 units). There were no significant differences in mortality (OR 1.49, 95% CI 0.67 to 3.29), but adverse events were significantly more common for participants treated with coils (OR 2.14, 95% CI 1.41 to 3.23). The quality of evidence ranged from low to high [10]. The most common adverse events associated with coil treatment are pneumonia (18–46%) [14, 15] and COPD exacerbation (10–87%) [16, 17], with other less common events including pneumothorax, chest pain, and hemoptysis.

**Bronchoscopic thermal vapour ablation**

The technique utilizes bronchoscopically applied heat water vapour delivered through a dedicated catheter system leading to a local inflammatory reaction and tissue damage. The result is fibrosis and local atelectasis thus causing the reduction in lung volume [1]. The STEP-UP study was a multicenter, RCT assessed result of...
BTVR in patients with predominantly upper lobe emphysema. The trial results documented a mean difference between the active treatment group and controls for FEV1 as +14.7% \((p < 0.001)\), for 6MWD as +30.5 m \((p = 0.06)\), for RV 0.30 L \((p = 0.015)\), and for the SGRQ score as -9.7 points \((p = 0.0021)\). There was no significant between-group difference in mortality \((OR 2.82, 95\% CI 0.13 to 61.06)\), but vapour ablation led to significantly more adverse events \((OR 3.86, 95\% CI 1.00 to 14.97)\) \[14\]. The adverse events mainly seen were excessive inflammatory response leading to cough, fever and dyspnea, pneumonia \((18\% - 23\%)\) \[18\], and COPD exacerbation \((9\% - 24\%)\) \[18, 19\].

### Lung sealant

The lung sealant (AirSeal) is a cross-linking compound made from aminated polyvinyl alcohol \((4.5\ mL, 2.1\% w/v)\) and glutaraldehyde \((0.5\ mL, 1.25\% w/v)\). These two compounds are mixed with air to create a foam which is then immediately delivered using a dedicated catheter via a bronchoscope to the desired segments. It mechanically closes off smaller airways and alveoli and locally blocks collateral channels preventing gas from entering the region and leading to absorption atelectasis \[1\]. The ASPIRE study, a multicenter RCT, evaluated 57 patients with advanced upper lobe predominant emphysema. Unfortunately, the study was stopped early due to financial reasons. That being said, the available data from 3 months of trials showed a median FEV1 improvement of +11.4% \((p = 0.0037)\) for the AirSeal treatment vs -2.1% in the controls \((p = 0.0037)\). The improvement in SGRQ score was significant \((-11 vs -4 points; p = 0.026)\). However, the number of adverse effects was greater in the treatment group \[15\]. Further studies using this methodology are currently withheld due to financial reasons and major concerns about post procedure inflammation related side effects. There is an ongoing trial NCT02877459 where the original method is redesigned into a sequential procedure to use \(20\% - 25\%\) of the original dosage.

### Airway bypass

In this technique, extra-anatomical (airway-bypass) passages are created using drug-eluting stents in order to empty the lungs on expiration \[1\]. The EASE trial, a multicenter RCT,
documented a significant improvement in pulmonary function on Day 1 of the procedure. At 6 months, no difference between treatment arms were noted with respect to the co-primary efficacy endpoint (30 of 208 for airway bypass vs 12 of 107 for sham control; posterior probability 0.749, below the Bayesian success threshold of 0.95) [16]. The immediate striking effects seen in these severely diseased emphysema patients nevertheless potentially point to airway bypass as a concept to investigate and develop further in the future. The summarized approach to bLVR is depicted in Figure 1.

**Conflict of interest**

None declared.

**References:**

1. Browning RF, Parrish S, Sarkar S, et al. Bronchoscopic interventions for severe COPD. J Thorac Dis. 2014; 6(Suppl 4): S407–S415,doi: 10.3978/j.issn.2072-1439.2014.08.20, indexed in Pubmed: 25337396.
2. Gülşen A. Bronchoscopic lung volume reduction: a 2018 review and update. Turk Thorac J. 2018; 19(3): 141–149,doi: 10.5152/TurkThoracJ.2018.18044, indexed in Pubmed: 30083406.
3. Sciurba FC, Ernst A, Herth FJF, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med. 2010; 363(13): 1233–44.
4. Vallipour A, Herth FJF, Burghuber OC, et al. Target lobe volume reduction and COPD outcome measures after endobronchial valve therapy. Eur Respir J. 2014; 44(2): 387–396,doi: 10.1183/09031936.00130212, indexed in Pubmed: 23845234.
5. Klooster K, ten Hacken NHT, Hartman JE, et al. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med. 2015; 373(24): 2325–2335, doi: 10.1056/NEJMoas1507097, indexed in Pubmed: 26650153.
6. Herth FJF, Noppen M, Vallipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J. 2012; 39(6): 1334–1342, doi: 10.1183/09031936.00161611, indexed in Pubmed: 22282552.
7. Vallipour A, Slebos DJ, Herth FJF, et al. Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT study. Am J Respir Crit Care Med. 2016; 194(9): 1073–1082,doi: 10.1164/rcrm.201607-136OC, indexed in Pubmed: 27580422.
8. Kemp SV, Slebos DJ, Kirk A, et al. A multicenter randomized controlled trial of zephyr endobronchial valve treatment in homogeneous emphysema (TRANSFORM). Am J Respir Crit Care Med. 2017; 196(12): 1535–1543,doi: 10.1164/rcrm.201707-192OC, indexed in Pubmed: 28688504.
9. Li S, Wang G, Wang C, et al. The REACH trial: a randomized controlled trial assessing the safety and effectiveness of the spiration® valve system in the treatment of severe emphysema. Respir. 2019; 97(5): 416–427,doi: 10.1159/000494327, indexed in Pubmed: 30554211.
10. Jen VA, Hnin K, Grosser D, et al. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. Cochrane Library. 23 February 2017 . Available at: https://www.cochranelibrary.com/cdr/home/10.1002/14651858.CD012158.pub2/full. [Last accessed: 26.10.2020].
11. Shah F, Zoumout Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. The Lancet Respiratory Medicine. 2013; 1(3): 232–240, doi: 10.1016/s2213-2600(13)70047-x.
12. Deslée G, Mal H, Dutau H, et al. Lung volume reduction coil treatment vs usual care in patients with severe emphysema: the REVOLENS randomized clinical trial. JAMA. 2016; 315(2): 175–184,doi: 10.1001/jama.2015.17921, indexed in Pubmed: 26757466.
13. Sciurba FC, Criner GJ, Strange C, et al. Effect of endobronchial coils vs usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial. JAMA.
14. Herth F, Shah P, Valipour A, et al. STEP-UP randomized controlled trial of vapor ablation in patients with severe emphysema: 12 month results. Interv Pulmonol. 2016, doi: 10.1183/13993003.congress-2016.oa475.

15. Come CE, Kramer MR, Dransfield MT, et al. A randomised trial of lung sealant versus medical therapy for advanced emphysema. Eur Respir J. 2015; 46(3): 651–662, doi: 10.1183/09031936.00205614, indexed in Pubmed: 25837041.

16. Shah PL, Slebos DJ, Cardoso P, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. The Lancet. 2011; 378(9795): 997–1005, doi: 10.1016/s0140-6736(11)61050-7.