Review Article | Surgery: Cardiothoracic Surgery

Bronchoscopic treatments of chronic obstructive pulmonary disease (COPD): a narrative review

Hasham Saeed[1], David M. Dibardino[2], Kevin C. Ma[2]^

[1]Department of Medicine, RWJBarnabas Health/Trinitas Regional Medical Center, Elizabeth, NJ, USA; [2]Division of Pulmonary, Allergy, and Critical Care, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Contributions: (I) Conception and design: DM Dibardino; (II) Administrative support: DM Dibardino, KC Ma; (III) Provision of study materials or patients: KC Ma; (IV) Collection and assembly of data: H Saeed; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kevin C. Ma, MD. Division of Pulmonary, Allergy, and Critical Care, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, 3400 Spruce St. Gates 8th Floor, Philadelphia, PA 19104, USA. Email: kevincma@outlook.com.

Background and Objective: Several procedural therapies have been described for patients with advanced chronic obstructive pulmonary disease (COPD) to date. The primary objective of this narrative review is to critically evaluate the effectiveness, safety, and long-term outcomes of these bronchoscopic and surgical interventions.

Methods: The databases that were mainly used to search relevant studies were Google Scholar, PubMed, EMBASE and Cochrane library from January 1950 to April 2023. Articles written in English language are included only.

Key Content and Findings: Lung volume reduction (LVR) surgery represents one of the first successful invasive options in patients with advanced heterogenous emphysema. This landmark surgical option demonstrated improvement in health status and lung function outcomes, but at the cost of significant morbidity and mortality. Various endobronchial procedures have been developed, one of which is endobronchial valves (EBV) placement for bronchoscopic LVR that have been extensively studied and have a potential to offer comparable outcomes with lower mortality and complication rates compared to surgical LVR. Several multicenter trials and studies have shown significant improvements in lung function, exercise capacity, and quality of life (QOL) with the use of EBV in patients with emphysema, although adverse events such as pneumothorax and pneumonia have been observed. Data regarding other modalities is evolving. For patients with chronic bronchitis, bronchial rheoplasty has shown significant improvements in QOL, reduced cough and phlegm production, and a decrease in goblet cell hyperplasia. Another procedure, metered cryospray, has demonstrated initial improvements in symptoms, but long-term efficacy is unproven. Clinical trials are underway to further evaluate its effectiveness. Lastly, for patients with frequent COPD exacerbations, targeted lung denervation has shown preliminary safety and efficacy in reducing respiratory events and COPD exacerbations. Ongoing clinical trials are underway that focus on the frequent exacerbation phenotype.

Conclusions: LVR surgery is deemed effective in carefully selected patients with severe emphysema but is associated with higher surgical risk and morbidity and mortality. Bronchoscopic interventions, particularly EBV, offers an attractive, comparatively lower risk, option for a greater group of patients with severe emphysema to achieve significant improvements in 6-minute walk distance, QOL, and pulmonary function tests.

Keywords: Chronic obstructive pulmonary disease (COPD); lung-volume-reduction surgery; bronchoscopic lung-volume-reduction; endobronchial valve (EBV)

^ ORCID: 0000-0002-0687-5401.

Received: 01 July 2023; Accepted: 02 February 2024; Published online: 26 April 2024.
doi: 10.21037/amj-23-100
View this article at: https://dx.doi.org/10.21037/amj-23-100

Introduction

Chronic obstructive pulmonary disease (COPD) is a common lung disease that is characterized by persistent respiratory symptoms (e.g., dyspnea, cough) and airflow limitation that is often progressive and not fully reversible (1). Pathophysiologically, COPD can be due to emphysema, chronic bronchitis, or both. In emphysema, enlargement of the airways distal to the terminal bronchioles is accompanied by destruction of airspace walls and alveolar tissue that leads to the loss of elastic recoil and bronchiolar collapse (2). The end result is airflow limitation, resting hyperinflation, and loss of gas exchanging surfaces (3). Chronic bronchitis is a result of chronic inflammation that causes mucous hypersecretion and narrowing of small airways (1). There are numerous environmental and molecular risk factors for the development of COPD, the most important of which is cigarette smoking (4). The management of COPD involves reversal of the risk factors and initiation of pharmacologic (e.g., bronchodilators, corticosteroids, etc.) and nonpharmacologic (e.g., pulmonary rehabilitation, oxygen supplementation, etc.) therapy (1). Patients with severe or end-stage COPD and impaired quality of life (QOL) despite maximal medical therapy can be considered, depending on their overall functional status, comorbidities, and fulfillment of eligibility criteria, for advanced treatments such as lung volume reduction (LVR) procedures, lung transplantation, or experimental treatments. This is because most of these interventions have shown improvement in QOL and functional status as discussed throughout the review. The aim of this review is to discuss the available surgical and bronchoscopic procedures for COPD and to critically evaluate the efficacy, safety, and long-term outcomes of these procedures. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-100/rc).

Methods

The databases that were mainly used to search relevant studies were Google Scholar, PubMed, EMBASE and Cochrane library from 01/01/1950 to 04/24/2023. Articles written in English language are included only. The search terms that were used included, but not limited to, surgical lung volume reduction, severe emphysema and surgery, lung-volume-reduction surgery, severe emphysema and bronchoscopy, bronchoscopic lung volume reduction, bronchoscopic lung-volume-reduction, lung coils and lung volume reduction, thermal vapor ablation and lung volume reduction, lung sealants and lung volume reduction, airway stents and lung volume reduction, chronic bronchitis and bronchoscopic treatment, cryotherapy and chronic bronchitis, lung denervation, among others (*Table 1*).

Surgical treatment of emphysema

The first attempt at surgical LVR was made by the American surgeon and anatomist Otto Brantigan in 1950s in 33 subjects with emphysema (5). He hypothesized that if a significant portion of abnormal lung tissue that is resulting in hyperinflation and impaired elastic recoil is removed, then the remaining lung volume will be able to fit the pleural space on full expiration, thus restoring the elastic recoil to some extent, and thereby improving airflow obstruction. LVR was obtained by resection and/or folding of the destroyed lung tissue. He also performed partial sympathectomy to reduce secretions based on findings from previous observations (6). In 1961, he published a case-series of 56 subjects who underwent unilateral and bilateral LVR surgery (7). The subjects had improvements in exercise tolerance, vital capacity and QOL as well as decline in morning cough and sputum production. However, due to limitations of surgical technology at the time, the overall operative mortality of 16% was considered prohibitive.

In 1997, Cooper *et al.* renewed interest in this procedure when they reported outcomes of 100 consecutive cases who underwent bilateral volume reduction via median sternotomy approach, with a mean age of 61 years and mean forced expiratory volume in the first second (FEV1) of 0.69 L (24% of predicted) (8). These subjects experienced an average increase of 400 mL in FEV1 and 600 mL in forced vital capacity (FVC) at 6-month follow-up, as well as a reduction in residual volume (RV) of approximately 2 L.

Table 1 The search strategy summary

Items	Specification
Date of search	04/24/2023
Databases and other sources searched	Google Scholar, PubMed, EMBASE, Cochrane
Search terms used	Lung volume reduction, lung volume reduction surgery, LVR, endobronchial valve, EBV, EBV and COPD, intrabronchial valve, IBV, IBV and COPD lung coils and COPD, LVRC, LVRC and COPD, Thermal Vapor Ablation, BTVA, BTVA and COPD, Lung sealants, ELS, ELS and COPD, Airway by-pass stents, Airway by-pass stents and COPD, Bronchial Rheoplasty, Bronchial Rheoplasty and COPD, Metered Cryospray, Metered Cryospray and COPD, Targeted Lung Denervation, TLD, TLD and COPD
Timeframe	January 1950 to April 24, 2023
Inclusion criteria	Only articles in English language are included. Studies that were included were case-series, randomized and non-randomized controlled trials
Selection process	After initial literature review, the list made by each author was discussed and narrowed down

LVR, lung volume reduction; EBV, endobronchial valve; COPD, chronic obstructive pulmonary disease; IBV, intrabronchial valve; LVRC, lung volume reduction coils; BTVA, bronchoscopic thermal vapor ablation; ELS, emphysematous lung sealant; TLD, targeted lung denervation.

Furthermore, exercise tolerance improved and a significant number of subjects no longer required oxygen therapy. The surgical intervention mainly targeted the upper lobes for tissue removal. The all-cause mortality rate after 1 year was 5%.

The initial reports by Cooper highlighted the importance of appropriate selection of patients who would benefit from surgical LVR and stimulated other cardiothoracic surgeons to perform LVR surgery. Several uncontrolled case series, small randomized controlled trials (RCTs), and prospective RCTs shed light on the role of surgical LVR in the management of advanced COPD. Most of these studies showed significant improvement in FEV1, FVC, total lung capacity (TLC), RV, gas exchange and QOL after surgical LVR but with associated moderate intraoperative mortality risk (9-12).

Despite some encouraging initial findings, several inquiries remained unresolved. The National Emphysema Treatment Trial (NETT), a comprehensive RCT, was published in 2003 to examine mortality effects, the size and endurance of benefits, and the criteria for selecting patients (13). The primary endpoints of the study were overall mortality and maximal exercise capacity. The trial registered 1,218 participants and revealed that, after 24 months, there was a significant improvement of over 10 W in exercise capacity for 15% of subjects in the surgery group, in comparison to 3% in the medical-therapy group (P<0.001). Subjects with upper-lobe predominant emphysema and low exercise capacity (<40 W in men, <25 W in women) demonstrated a survival benefit while subjects with non-upper-lobe emphysema and high baseline exercise capacity exhibited an increased risk of mortality and insignificant functional improvement. The surgical group had an overall 90-day mortality rate of 7.9%, in contrast to 1.3% in the medical care group (P<0.001). In 70 subjects with FEV1 <20% predicted and either homogeneous emphysema or diffusing capacity of lung for carbon monoxide (DLCO) <20% predicted, a high risk for postoperative death (28.6%) was detected during an interim analysis.

A review conducted in 2016 established that LVR surgery could result in improved health status and lung function outcomes for patients suffering from severe upper lobe-predominant emphysema and low exercise capacity (14). Nevertheless, the authors acknowledged the risks associated with the procedure, including early mortality and adverse events. The use of LVR surgery in potential lung transplant patients has been studied. In patients fulfilling criteria for lung transplantation, it was found to potentially defer transplantation for up to 5 years and did not seem to impair the chances for subsequent successful lung transplant (15). Moreover, LVR surgery has been studied in patients with unilateral lung transplant for the treatment of native lung hyperinflation (NLH). Since it results in improvement in thoracic overdistention, LVR surgery was shown to result in improved exercise capacity by improving mean oxygen

consumption to 35% (16). However, the procedure is associated with major risks of peri-operative infections in these immunosuppressed patients. In addition, certain immunosuppressants are associated with poor wound healing that can delay recovery.

Various centers across the globe presently provide LVR surgery. However, several factors play a role in underutilization of LVR surgery, ranging from restricted patient access, lack of awareness of therapeutic benefits of the procedure by physicians in the appropriate population, perceived high risk and high cost of the procedure and availability of bronchoscopic LVR, among others (17,18). Several LVR programs have a dedicated emphysema multidisciplinary team (MDT), which works towards appropriate case selection, providing assistance in overcoming socioeconomic barriers and maximizing pre- and post-surgical care to have the best possible outcomes (19).

Bronchoscopic treatment of emphysema

The experience gained from the evolution of LVR surgery shows that certain cases of emphysema may improve through interventions aimed at restoring chest geometry and respiratory mechanics. This can theoretically be done either by closing anatomical airway passage to the destroyed segments of the lung or by opening extra-anatomical airway passage to allow trapped gas to exit from hyperinflated areas of the lungs. To mitigate the risks associated with LVR surgery, a variety of endobronchial procedures were developed in an effort achieve comparable outcomes with a favorable mortality and complications rates compared to surgical LVR. One such procedure is endobronchial valve (EBV) placement to achieve bronchoscopic LVR.

EBVs

The first experience of endoscopic LVR was reported in 2003 by Sabanathan *et al.* (20). Initially, detachable silicone balloons filled with contrast medium were deployed into the airways to achieve endobronchial blockade of the destroyed segments. However, these proved to be inadequate due to migration issues, and they were subsequently replaced with locally manufactured Gianturco-type stents made of stainless steel, incorporating a biocompatible sponge to produce blockage. Their study involved eight participants, comprising five males and three females with severe disease. While five of the subjects experienced immediate improvements in their breathing difficulties, spirometry and lung volume results were inconclusive. Additionally, four participants displayed minor reductions in thoracic distension, and chest radiographs revealed increased diaphragmatic curvature. Immediate complications included periprocedural hypoxia in two cases, an immediate post-procedural occurrence of bilateral tension pneumothoraces in one case, severe bronchospasm in one case, and pneumonia in two cases. Importantly, there was no stent migration, but one instance of stent disintegration due to metal fatigue occurred after 1 year.

These devices were then further refined to incorporate a one-way valve to vent the air to achieve iatrogenic atelectasis, clearance of secretions, prevention of infections, and enhance long-term safety. Snell *et al.* and others conducted multiple human pilots with these valves in patients with upper lobe predominant disease and found significant improvements in FEV1, DLCO and reduction in regional volume of computed tomography (CT) scans (21-23). However, moderate risk of distal pneumonia or pneumothorax remained.

A multicenter RCT was performed in 2000s called the endobronchial Valve for Emphysema palliatioN Trial (VENT) to determine the safety and efficacy of unilateral treatment of advanced heterogenous emphysema with Zephyr (Pulmonx Corp, Redwood City, CA, USA) EBV compared to standard medical care (220 EBV *vs.* 101 control) (24). Subjects were carefully selected based on pulmonary function tests (PFTs), 6-minute walk distance (6MWD), DLCO and quantitative and visual indexes of the severity of lobar emphysema and fissure integrity on high-resolution CT (HRCT). Statistically significant improvements were noted in primary endpoints like FEV1 (mean between-group difference of 6.8%, P=0.005), 6MWD (median between-group difference of 5.8%, P=0.04) and QOL, though the clinical magnitude of the results was modest. Small improvements have also been noted in secondary outcomes like mean St. George's Respiratory Questionnaire (SGRQ) and Modified Medical Research Council (mMRC) scale. The improvements were linked to high inter-lobar heterogeneity of emphysema and fissure integrity as evaluated by HRCT. Expansion in the volume of the adjacent healthy lobes was enhanced in subjects with complete fissures. During the post-implantation follow-up, cases of hemoptysis and COPD exacerbations were more common in the group that received EBV. Moreover, 7.5% of patients were found to have device-related adverse events.

Following the VENT study, another European single-center RCT called BeLieVeR-HIFi was published in 2015 (25). It enrolled patients with heterogenous emphysema, with the target lobe having intact inter-lobar fissures on chest CT. Although only CT scan findings were used to determine target lobe selection, measurements of collateral ventilation using Chartis® balloon catheter system (Pulmonx Corp) were made to compare the accuracy of the two approaches. Subjects were randomly assigned to receive Zephyr® EBV valves along with medical therapy or sham bronchoscopy along with medical therapy. The outcomes were similar to the VENT study in terms of PFTs and exercise capacity. In the intervention group, FEV1 increased by a median 8.77% [interquartile range (IQR), 2.27–35.85%] *vs.* 2.88% (IQR, 0–8.51%) in the control group (P=0.0326). In addition, 6MWD increased by 25 m in the intervention group, compared to 3 m in the control group (P=0.01). However, serious adverse events occurred more frequently in the EBV group, and there were two deaths (8% of subjects in the EBV group).

Inspired by the findings of BeLieVeR-HIFi study, another single-center RCT called STELVIO was published later in 2015 in which patients with both homogenous and heterogenous emphysema were included (26). The target lobe selection was determined by the measurements obtained from the Chartis® balloon catheter system which provided better analysis of fissure integrity. Subjects were randomly assigned to receive Zephyr® EBV valves along with medical therapy or medical therapy alone. Improvements in PFTs and exercise capacity were statistically significant. Adverse events occurred more frequently in the treatment group and there was one death (3% of subjects in the EBV group).

These studies made researchers realize the significance of fissure integrity and accurate assessment of collateral ventilation in conjunction with severe hyperinflation, resulting in the emergence of successful RCTs akin to the IMPACT study in 2016 (27). The IMPACT RCT showed improvement in PFTs, 6MWD and QOL in patients with homogenous emphysema after the application of Zephyr EBV. Moreover, TRANSFORM [2017] (28) and LIBERATE [2018] (29). RCTs reproduced the findings in patients with heterogenous emphysema. In the TRANSFORM RCT, the mean ± SD change in FEV1 at 6 months was 20.7%±29.6% in the intervention group as compared to –8.6%±13.0% in the control group (mean between-group difference of 29.3, P<0.001). Moreover, 6MWD improved by 36.2±76.9 m in the intervention group as compared to –42.5±68.2 m in the control group at 6 months (mean between-group difference 78.7 m, P<0.001). In LIBERATE RCT, the mean ± SD change in FEV1 at 12 months was 17.16%±27.93% in the intervention group as compared to –0.80±26.94 in the control group (mean between-group difference of 17.96, P<0.001). In addition, 6MWD improved by 12.98±81.54 m in the intervention group as compared to –26.33±81.50 m in the control group at 12 months (mean between-group difference 39.31 m, P<0.002). Statistically significant improvement in SGRQ, mMRC scale and BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index were also seen, with pneumothorax being the most common adverse event (29.2% and 26% of the EBV subjects).

Another type of valve called intrabronchial valve (IBV) by Spiration Inc. has demonstrated efficacy in similar patient populations. In 2019, REACH trial was performed in which 107 subjects with heterogeneous emphysema and intact fissure (based on HRCT findings) were randomized to IBV *vs.* control group (30). The 3-month follow-up showed significant improvements in FEV1, successful target LVR, exercise tolerance and QOL in the treatment group. The findings were the same as that seen in EMPROVE trial that came out in the same year in which 172 participants were randomized to the treatment *vs.* control group (31).

Improvements in REACH and EMPROVE were more modest than those seen in LIBERATE and TRANSFORM. In REACH, 41% in the IBV group had ≥15% improvement in FEV1 at 6 months compared to 21% of controls. The mean improvement in FEV1 at 6 months was 0.091 L in the IBV group *vs.* –0.024 L in the control arm. In LIBERATE, 49% in the EBV group had >15% improvement FEV1 at 6 months compared to 12% of controls. The mean improvement in FEV1 at 6 months was 0.130 L in the EBV group *vs.* 0.003 L in the control group. These differences may be partly explained by differences in rates of meaningful target LVR. At 6 months, 66% of IBV subjects achieved target lobe volume reduction of ≥350 mL in REACH compared to 79% of EBV subjects in LIBERATE. One potential explanation is that the IBV system utilizes only radiographic assessment of fissure integrity without the additional tool of direct collateral ventilation measurement being performed in the later EBV studies.

Recently, the CELEB study group conducted a 12-month RCT comparing LVR surgery and bronchoscopic LVR via EBV in patients with emphysema (32). The aim was to determine if unilateral LVRS was superior to EBV. However, the results showed that both treatments led to

similar improvements in lung function, exercise capacity, and overall QOL. Survival rates were similar in both groups, with one death in each arm over the 12-month study period (33).

Lastly, EBVs and IBVs have also been used for the treatment of severe NLH in patients with single lung transplant. A case-series was published in which 4 patients with NLH were treated with EBV (34). Three of the four patients demonstrated improvement in PFTs, at least initially. The patient who did not show improvement was suggested to have greater degree of collateral ventilation on CT or because of the fact that he had pleurodesis in the past that could have prevented volume changes. However, only two of the four patients reported some improvement in exercise tolerance. In a study which used IBV in 14 such patients, their use showed significant improvements in FEV1 of 9% (P=0.013) and FVC of 15% (P=0.034) after a month of their deployment (35). Three of them were hospitalized for an infection 2 months after treatment and another two had pneumothorax, demonstrating acceptable safety.

Lung coils

Lung or endobronchial coils are metallic devices made of nitinol that can be placed through the working channel of flexible bronchoscope. They work by compressing the lung parenchyma that is not involved in gas exchange, thereby improving hyperinflation and restoring some of the lung tissue tension (36).

In 2013, a multicenter UK-based RCT (RESET) was performed, in which 47 subjects were randomized to treatment *vs.* usual care (37). Subjects were not excluded based on distribution of the disease. The study found significant improvement in SGRQ and 6MWD in the treatment group with no between-group difference in serious adverse events. This was followed by another multicenter RCT named the REVOLENS study in 2016 in which 100 subjects were randomized to treatment *vs.* usual care (38). The primary endpoint was a minimal clinically important difference (MCID) of 54 m in the 6MWD after a period of 6 months, utilizing a one-sided hypothesis test. The primary endpoint was achieved in 18 patients (36%) in the coil group and 9 patients (18%) in the usual care group, with a between-group difference of 18% (P=0.03). However, the improvement in 6MWD in the treatment group overall was only marginally significant (18 *vs.* −3 months, P=0.06). Moreover, statistically significant improvement in SGRQ was also noted (−11.1 *vs.* 2.3, P<0.001).

In the RENEW trial conducted in 2016, the efficacy and safety of coils were evaluated in 315 subjects from 21 North American and 5 European centers (39). The subjects were randomized in a 1:1 fashion to receive coils *vs.* usual care. In the treatment group, each subject underwent two sequential procedures 4 months apart. The primary efficacy endpoint was the absolute change in 6MWT at 12 months from the baseline, with a MCID defined as 25 m. The coil group showed a statistically significant improvement in 6MWD and in FEV1 and SGRQ and 40% of subjects in the coil group demonstrated MCID, compared to 26.9% in the usual care group (P=0.01). The coil group had a higher incidence of major complications, with 34.8% of participants experiencing potentially life-threatening or fatal events compared to 19.1% in the usual care group (P=0.002). This difference was mainly due to a higher incidence of lower respiratory tract infections in the coil group (18.7% *vs.* 4.5%; P<0.001). Additionally, there were two cases of hemoptysis requiring intervention in the coil group. However, no significant differences in other major complications were observed between the two groups.

Lung coils are currently not approved for clinical use in the United States but are available in Europe. Overall the benefits are modest and the increased incidence of pneumonia makes this a less attractive option than EBVs. However, lung coils do not require intact fissures and thus are an option for patients with collateral ventilation.

Thermal vapor ablation

Bronchoscopic thermal vapor ablation (BTVA) therapy delivers high-temperature steam/water vapors into the target lung to induce inflammatory reaction and resultant fibrosis (40).

In 2012, a study performed by Snell *et al.* included 44 subjects from Europe and USA with heterogenous upper-lobe predominant emphysema (41). The subjects were treated with BTVA at a dose of 10 cal/g tissue. Significant improvements in FEV1, FVC, RV, QOL, dyspnea index and 6MWD were noted. Moreover, lobar volume was reduced by up to 48% in follow-up HRCT. Major complications were COPD exacerbations (n=10), pneumonia (n=6), respiratory tract infections (n=5) and hemoptysis (n=3), all of which improved with medical therapy except in 1 case with COPD exacerbation who died 67 days after the treatment. The total number of adverse events in the treatment group was 29 (65.9%), 25 (86.2%)

of which were respiratory in origin and could be related to the procedure. Fissure integrity appeared to have no bearing on treatment response (42).

In 2016, a multicenter RCT (STEP-UP) was published in which 70 subjects were randomized to staged bilateral BTVA treatment (n=46) *vs.* control group (n=24) in 13 European and 3 Australian centers (43). These subjects had both complete and incomplete fissures. Although significant improvements were noted in FEV1, FVC and SGRQ, the treatment group experienced more COPD exacerbations, a case of pneumonia and hemoptysis requiring admission to intensive care unit (ICU) and a death possibly related to BTVA when compared with control group. Reduction in RV (mean difference of 237 mL compared to control group; P=0.07) was noted along with CT evidence of volume reduction of the treated segments. No significant improvement in 6MWD was noted.

BTVA is currently not available in the United States but is available in Europe. Similar to lung coils, the increased complications rate with BTVA has prevented this technique from gaining widespread acceptance. However, BTVA allows for segmental treatment of emphysema that may be beneficial in patients with intralobar heterogeneity in emphysema. BTVA technology is also currently being explored as a treatment technique for localized cancers in the lung (44).

Lung sealants

The initial generation of sealants were biological materials designed to induce atelectasis and subsequently promote fibrosis in the specific lung tissue being targeted. In the first human study in 2009, 50 subjects with heterogenous upper-lobe predominant emphysema underwent the treatment (45). A fibrinogen biopharmaceutical suspension and thrombin solution were bronchoscopically instilled for the treatment, which polymerized in the affected area to create a hydrogel. This hydrogel caused a localized inflammatory reaction that resulted in the collapse of the lung region over a period of 4–6 weeks. The trial showed some improvements in RV/TLC ratio, FEV1, FVC and 6MWD.

The biological substance was then replaced by synthetic polymeric foam by Aeris Therapeutics. Following its preliminary study (46), the ASPIRE RCT was performed in 2012 to evaluate the AeriSeal treatment in subjects with severe upper-lobe predominant emphysema (47). The trial, which aimed to enroll 300 subjects, was terminated prematurely due to financial reasons after randomizing 95 subjects. Improvements were noted in the treatment group in FEV1, SGRQ, 6MWD and upper lobe volume at 6 months. Nevertheless, 44% of treated subjects had major complications requiring hospitalization and two procedure-related deaths, making it unsuitable for direct LVR. A major criticism of the study was the high dose of sealant used per subject.

The technology was acquired by Pulmonx corporation and a multi-center single-arm study (CONVERT) is evaluating the use of AeriSeal System in occluding collateral air channels in a target lung lobe in patients with severe emphysema and poor fissure integrity (48). Subjects with successfully occluded collateral ventilation will then undergo Zephyr EBV insertion. An interim analysis of 32 subjects demonstrated a 82% success rate in converting subjects with initially detectable collateral ventilation to no collateral ventilation on 45-day followup reassessment, allowing for subsequent treatment with EBVs (49). This technique may allow significantly more patients to under bronchoscopic LVR with EBVs. For example, in the LIBERATE trial, 255 subjects underwent bronchoscopic collateral ventilation assessment with the Chartis© catheter and 65 (25%) were found to have collateral ventilation (29).

Airway by-pass stents

Airway by-pass aims at creating extra-anatomical transbronchial passages between the hyperinflated lung parenchyma and larger airways. Using paclitaxel-eluting stents to facilitate expiration, the stents decrease air trapping and induce pulmonary deflation (50). In the initial multicenter human study, 35 individuals with severe homogenous emphysema underwent a total of 264 stent implantations, with a median of 8 stents per patient. The one-month follow-up analysis revealed a significant reduction in RV and improvements in FEV1, VC, and 6MWD (51). However, by the 6-month mark, functional parameters began to revert towards their baseline values, with only changes in RV and the dyspnea index remaining statistically different from the baseline. The long-term benefits were most pronounced in individuals with a high degree of hyperinflation (RV/TLC >0.067). One incidence of fatal hemoptysis was reported.

In 2011, a randomized, multicenter, sham-controlled EASE trial was published involving 315 subjects with severe emphysema and hyperinflation (RV/TLC >0.65) (52). Participants were randomized 2:1 to airway by-pass

(n=208) and sham control (n=107). No statistically significant improvements were observed in FEV1, FVC, RV, 6MWD, SGRQ or mMRC at 3, 6 or 12 months. One periprocedural death secondary to ruptured aortic aneurysm, one periprocedural massive hemoptysis, one event of respiratory failure requiring mechanical ventilation and two pneumothoraces requiring drainage were reported in the treatment group. COPD exacerbations were also more common in the treatment group compared to sham-control. In subjects with severe homogeneous emphysema, airway bypass was associated with increased risks and no long-term or sustainable benefit.

Due to the lack of sustained symptom improvement in heterogenous disease, and lack of benefit in homogenous disease, this technique was not pursued further.

All the relevant findings are summarized in *Table 2*.

Our approach to the assessment of patients for LVR

Patients with severe emphysema should meet specific criteria before undergoing a LVR procedure. First and foremost, they must be non-smokers or have quit smoking for more than 4 months, as continued smoking could compromise the success of the procedure (53). Patients should have a PFTs within the past year, with a preference for the last 6 months, with lung volumes performed by plethysmography. Patients must show a RV ≥150% of predicted and TLC ≥100% of predicted (53). A CT scan of the chest without intravenous contrast with 1mm cuts from the last year (preferably the last 6 months) should reveal no suspicious nodules, fibrosis, or other lung pathology that may be a major contributor to the patients symptoms (53). Quantitative analysis of lobar emphysema should demonstrate adequate destruction in the target lobe and bordering fissures should demonstrate adequate integrity (25-27,30). Patients should exhibit symptomatic (the mMRC dyspnea scale should indicate a score greater than 2), but stable COPD, defined as experiencing fewer than two exacerbations annually, being on optimal inhaler therapy, and having a low mucous burden. In our experience, patients with prominent chronic bronchitis symptoms with persistent wheezing, exacerbations, and mucous production do poorly with bronchoscopic LVR with EBVs despite evidence of hyperinflation and air-trapping on PFTs.

Transthoracic echocardiography (TTE) should rule out pulmonary hypertension (PH) and significant left ventricular ejection fraction (LVEF) depression (LVEF <45%). Room air arterial blood gas (ABG) and co-oximetry readings should indicate a pO_2 greater than 45 mmHg and a pCO_2 less than 60 mmHg (13). Lastly, a SPECT/CT perfusion scan should be considered to assess lung perfusion, with optimal lobar targets receiving less than 20% of total blood flow. These comprehensive criteria ensure that patients referred for LVR procedures are well-suited candidates, maximizing the likelihood of a successful outcome. In select circumstances we override certain criteria above if we believe there is reasonable clinical rationale to proceed and after a full discussion of potential risks and benefits with the patient.

Bronchoscopic treatment of chronic bronchitis

Bronchial rheoplasty

Bronchial Rheoplasty is a novel treatment modality that uses a catheter with a unipolar electrode to deliver short bursts of high-frequency electrical energy to the target tissue, resulting in reduction in goblet cell hyperplasia (GCH) (54).

Two combined multicenter single-arm clinical trials evaluated this treatment in 30 subjects with severe chronic bronchitis (55). Significant improvements were noted in QOL as measured by the COPD Assessment Test (CAT) and SGRQ. Cough and phlegm production was decreased. Moreover, there was a 39% relative reduction in mean GCH score as measured by pre- and post-procedure endobronchial biopsies. Four procedure-related adverse events were reported (pneumonia 1, COPD exacerbations 2 and mucosal scarring 1; all resolved with conservative measures).

Another prospective, randomized, parallel group, double-blind, sham-controlled, multicenter clinical trial following patients to 2 years has finished enrollment and is currently in the follow up phase (NCT04677465, Rhesolve). With a sample size of 270, subjects are randomized to staged bilateral bronchial rheoplasty *vs.* sham procedure in a 2:1 fashion. The primary outcome measure is mean change in CAT score at 6 months from baseline. Secondary outcome measures are change from baseline distal airway volume (DAV) at expiration using HRCT scans, rate of moderate and severe COPD exacerbations within 12 months, change from baseline in mean GCH score and change from baseline in cough frequency.

Table 2 RCTs for bronchoscopic interventions of severe emphysema

Trial	Technique	Emphysema distribution	Fissure integrity assessment	Primary outcome and time frame	Change from baseline						Pneumonia rate, n	Pneumothorax rate, n
					FEV1		6MWD		SGRQ score			
					Mean, mL (%)	Between group difference (P value)	Mean, m (%)	Between group difference (P value)	Mean	Between group difference (P value)		
VENT [2010] (24)	EBV *vs.* SMC	Heterogenous	HRCT	FEV1 and 6MWD at 6 months	34.5 (4.3) *vs.* −25.4 (−2.5)	60 (0.002)	Median: 9.3 (2.5) *vs.* −10.7 (−3.2)	19.1 (0.02)	−2.8 *vs.* 0.6	−3.4 (0.04)	7 *vs.* 2	9 *vs.* 0
BeLieVeR-HIFi [2015] (25)	EBV *vs.* sham bronch	Heterogenous	HRCT	FEV1 at 3 months	60 (8.7) *vs.* 30 (2.88)	30 (0.02)	Median: 25 *vs.* 3	22 (0.01)	−4.4 *vs.* −3.57	−0.83 (0.3)	2 *vs.* 0	2 *vs.* 1
STELVIO [2015] (26)	EBV *vs.* SMC	Homogenous & heterogenous	HRCT + Chartis	FEV1, FVC & 6MWD at 6 months	161 (20.9) *vs.* 21 (3.1)	140 (0.002)	60 (19.6) *vs.* −14 (−3.6)	74 (<0.001)	−21.8 *vs.* −7.6	−14.7 (<0.001)	2 *vs.* 1	6 *vs.* 0
IMPACT [2016] (27)	EBV *vs.* SMC	Homogenous	Chartis	FEV1 at 3 months	100 *vs.* −20	120 (<0.0001)	22.6 *vs.* −17.3	40 (0.002)	−8.63 *vs.* 1.01	−9.64 (<0.0001)	0 *vs.* 1	12 *vs.* 0
TRANSFORM [2017] (28)	EBV *vs.* SMC	Heterogenous	HRCT + Chartis	FEV1 at 3 months (following values at 6 months)	140 (20.7) *vs.* −90 (−8.6)	29.3 (<0.001)	36.2 *vs.* −42.5	78.7 (<0.001)	−7.2 *vs.* −0.7	−6.5 (0.031)	6 *vs.* 1	15 *vs.* 0
LIBERATE [2018] (29)	EBV *vs.* SMC	Heterogenous	Chartis	FEV1 at 12 months	104 (17.1) *vs.* −3 (−0.8)	107 (<0.001)	12.9 *vs.* −26.3	39.3 (0.002)	−7.5 *vs.* −0.5	−7.05 (0.004)	8 *vs.* 5	42 *vs.* 0
REACH [2019] (30)	IBV *vs.* SMC	Heterogenous	HRCT	FEV1 at 3 months	104 *vs.* 3	101 (0.001)	27.1 *vs.* 7.5	19.6 (0.12)	−7.92 *vs.* −0.73	−7.19 (0.058)	1 *vs.* 0	4 *vs.* 0
EMPROVE [2019] (31)	IBV *vs.* SMC	Heterogenous	HRCT	FEV1 at 6 months	99 *vs.* −2	101	−4.4 *vs.* −11.3	6.9	−8.1 *vs.* 4.8	−13	1 *vs.* 0	33 *vs.* 0
RESET [2013] (37)	LVRC *vs.* SMC	Homogenous & heterogenous	HRCT	SGRQ at 3 months	(14.19) *vs.* (3.57)	10.62% (0.03)	51.15 *vs.* −12.39	63.5 (<0.001)	−8.11 *vs.* 0.25	−8.36 (0.04)	Not reported	2 *vs.* 0
RENEW [2016] (39)	LVRC *vs.* SMC	Homogenous & heterogenous		6MWD at 12 months	(3.8) *vs.* (−2.5)	7 (<0.001)	Median: 10.3 *vs.* −7.6	14.6 (0.02)	−8.1 *vs.* 0.8	−8.9 (<0.001)	31 *vs.* 7	15 *vs.* 1
STEP UP [2016] (43)	BTVA *vs.* SMC	Heterogenous	Not reported	FEV1 and SGRQ at 6 months	(8.2) *vs.* (−1.8)	80.5 (10.1%) (0.004)	Not reported	29.4 (0.07)	−7.2 *vs.* −0.6	−6.6 (0.02)	17 *vs.* 2	2 *vs.* 0
ASPIRE [2012] (47)	ELS *vs.* SMC	Heterogenous	HRCT	FEV1 at 12 months (following values at 6 months)	(52.4) *vs.* (15.4)	37% (0.068)	Not reported	Not reported	Not reported	Not reported	15 *vs.* 2	1 *vs.* 0
EASE [2011] (52)	Airway bypass *vs.* sham bronch	Homogenous	HRCT	FVC and mMRC at 6 months	−10 *vs.* −20	−10 (0.4)	Not reported	Not reported	Not reported	Not reported	Not reported	3 *vs.* 1

RCTs, randomized controlled trials; FEV1, forced expiratory volume in the first second; 6MWD, 6-min walk distance; SGRQ, St. George's Respiratory Questionnaire; EBV, endobronchial valve; SMC, standard medical care; HRCT, high-resolution computed tomography; FVC, forced vital capacity; IBV, intrabronchial valve; LVRC, lung volume reduction coil; BTVA, bronchoscopic thermal vapor ablation; ELS, emphysematous lung sealant; mMRC, modified Medical Research Council dyspnea scale.

Metered cryospray

Metered cryospray works on the principle of destroying hyperplastic goblet cells and excess submucous glands with a liquid nitrogen spray to induce a nonscarring healing response in the airways. Early feasibility and safety studies on animal models and human subjects with nonchronic bronchitis demonstrated no device-related serious adverse events, intraoperative complications or technical difficulties (56,57). In 2020, Garner *et al.* published the results of a prospective, single-arm, open-label trial, in which 34 subjects underwent the treatment in three separate procedures (58). After three months, there was an improvement in SGRQ of –6.4 (95% CI: –11.4 to –1.3; P=0.01), in CAT of –3.8 (95% CI: –6.4 to –1.3; P<0.01) and in Leicester Cough Questionnaire of 21.6 (95% CI: 7.3 to 35.9; P<0.01), although no clinically relevant improvements were observed at 12 months. Secondary analysis noted subjects with baseline SGRQ score >50 had great improvements in SGRQ score post-procedure (up to –15.4).

Currently a phase III clinical trial (NCT03893370, SPRAY-CB) is recruiting. Inclusion criteria is modified compared to that of the Garner *et al.* study to only include subjects with a baseline SGRQ score of >50. The primary outcome measure is a change in SGRQ score from baseline to 12 months. A second study, which plans to involve 32 subjects (NCT03892694), is a RCT that will likely study the treatment's mechanisms of action in greater detail, with the end-point being goblet cell density at 6-month follow-up.

Both technologies aim to achieve improvement in chronic bronchitis symptoms through killing of mucosa globet cells, though in very different techniques. Interestingly, each company has constructed their phase III trials differently with different inclusion criteria. Overall published efficacy may be due to study population differences rather than any evidence of a superior technology.

Bronchoscopic treatment for prevention of COPD exacerbations-targeted lung denervation (TLD)

TLD is a technique in which a dual cooled radiofrequency catheter is used to disrupt parasympathetic nerve transmission, thereby depressing airway smooth muscle contraction and mucus production (59). In 2015, a feasibility study was performed in 22 subjects (59). Initially, 12 subjects received the treatment with 20 watts (W) energy in multiple rotational positions per bronchus through a dual-cooled catheter except for posteromedial aspect of the left bronchus where the power was reduced to 15 W due to proximity to the esophagus. To address local airway effects, the protocol was modified, and additional 12 patients underwent treatment with the electrode placed more distally to avoid delicate carina tissue. Moreover, a lower energy level of 15 W was used throughout. The treatment was staged, with each bronchus receiving TLD 30 days apart. Overall, the treatment was found to be safe, feasible and well-tolerated. However, one patient treated with 15 W energy had gastroparesis as a serious device related adverse event. The improvements were more significant in subjects treated with the higher dose (20 W). A sub-study performed on 7 subjects exhibited a reduction in inflammatory markers in bronchial wash and brush specimens 30 days after treatment (60). A subsequent analysis of the same cohort revealed that when combined with inhaled long-acting muscarinic antagonists, TLD treatment had a synergistic bronchodilatory effect (61). The safety of this procedure done in a single session was confirmed on a follow-up study, showing no device related complications up to 3 years after treatment (62).

In 2019, AIRFLOW1 was performed to determine the safety, feasibility, and dosing (29 *vs.* 32 W) of a second-generation TLD device (63). In the early phase, the trial was stopped due to excess gastric adverse event (e.g., delayed gastric emptying). Safety modifications were made to the technique, including use of an esophageal balloon to measure esophageo-to-electrode distance to avoid inadvertent capture of the gastric parasympathetic plexis. An additional 16 subjects were added to the sample size of 30 due to these adverse events. The study found no significant differences in safety or efficacy between the two different doses tested, although the higher-energy dose group (32 W) demonstrated a tendency towards greater efficacy. Clinically meaningful improvements were noted in the SGRQ-C (57% of subjects with ≥4 point drop) and CAT (79% of subjects with ≥2 point drop) score at 1 year but were not statistically significant.

The follow-up study, the AIRFLOW-2, involved 82 subjects, including those of AIRFLOW1, in a multicenter, randomized, double-blinded, sham-controlled trial (64). The results of the trial after 1 year showed that the TLD treatment group had significantly fewer respiratory events (32% *vs.* 71%; P=0.008) and a significantly lower risk of COPD exacerbation that required hospitalization (HR, 0.35; P=0.039) compared to the sham

group. Both AIRFLOW1 and 2 excluded subjects with a history of recurrent infections and/or COPD exacerbations.

AIRFLOW-3 is currently on-going (NCT03639051), with a specific focus on subjects with frequent exacerbations. The trial is a multicenter, double-blind, sham-controlled study to evaluate safety and efficacy (in preventing moderate to severe COPD exacerbation) after TLD. The planned sample size is 480 participants with equal allocation (1:1) in two arms.

There is considerable overlap between patients with frequent exacerbations as well as patients with prominent chronic bronchitis symptoms. There is currently no data on whether goblet cell directed therapies or targeted lung denervation will provide better improvement in patient QOL and whether the techniques are additive.

Conclusions

While surgical LVR remains the only LVR technique with a demonstrated benefit in randomized controlled studies, the target population is restricted to a small subgroup of patients struggling with a highly symptomatic and progressive disease. Moreover, many patients are hesitant to proceed with a procedure associated with a high morbidity and mortality where results are irreversible but improvement is not guaranteed.

Bronchoscopic LVR offers an attractive, comparatively lower risk, option for a greater group of patients with severe emphysema. EBVs remain the only option available in the United States but lung coils and vapor ablation may be considered in Europe for patients with evidence of collateral ventilation. The recently published preliminary data for the CONVERT study may allow for more patients to undergo bronchoscopic LVR with EBVs in the future.

We recommend all patients with symptomatic COPD with evidence of air trapping (RV ≥150% of predicted), hyperinflation (TLC ≥100% of predicted), and moderate to advanced emphysema be referred for evaluation for LVR.

For patients with severe chronic bronchitis, bronchial rheoplasty and cryotherapy show promising results and long-term data of more studies with adequate sample size should be able to determine reproducibility of efficacy. Phase III trials are currently ongoing and such patients can be considered for enrolment.

Lastly, for patients with recurrent COPD exacerbations requiring hospitalizations, TLD shows promise but more trials in the key target population is currently ongoing.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Jonathan Kurman and Bryan S. Benn) for the series "Diagnostic & Therapeutic Bronchoscopy" published in *AME Medical Journal*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-23-100/rc

Peer Review File: Available at https://amj.amegroups.com/article/view/10.21037/amj-23-100/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-23-100/coif). The series "Diagnostic & Therapeutic Bronchoscopy" was commissioned by the editorial office without any funding or sponsorship. D.M.D. reports that research contract from Gala Therapeutics was paid to his institution. D.M.D. received consulting fees from Olympus. K.C.M. reports that research contract from Right Air Inc. was paid to his institution. K.C.M. received consulting fees from Pulmonx Inc. and advisory board fees from Polarean Inc. and Verona Pharmaceutical. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. 2023 GOLD Report. Available at: https://goldcopd.org/2023-gold-report-2/
2. Rennard SI. COPD: overview of definitions, epidemiology, and factors influencing its development. Chest 1998;113:235S-41S.
3. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med 2011;365:1567-75.
4. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166:675-9.
5. Brantigan OC, Mueller E, Kress MB. A surgical approach to pulmonary emphysema. Am Rev Respir Dis 1959;80:194-206.
6. Kaunitz VH, Andersen MN. An experimental study of the effect of parasympathetic denervation of the lung on pulmonary artery pressure. J Thorac Surg 1954;27:55-61; discussion 61-3.
7. Brantigan OC, Kress MB, Mueller EA. The Surgical Approach to Pulmonary Emphysema. Diseases of the Chest 1961;39:485-99.
8. Cooper JD. The history of surgical procedures for emphysema. Ann Thorac Surg 1997;63:312-9.
9. Criner GJ, Cordova FC, Furukawa S, et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:2018-27.
10. Geddes D, Davies M, Koyama H, et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. N Engl J Med 2000;343:239-45.
11. Goldstein RS, Todd TR, Guyatt G, et al. Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. Thorax 2003;58:405-10.
12. Hillerdal G, Löfdahl CG, Ström K, et al. Comparison of lung volume reduction surgery and physical training on health status and physiologic outcomes: a randomized controlled clinical trial. Chest 2005;128:3489-99.
13. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059-73.
14. van Agteren JE, Carson KV, Tiong LU, et al. Lung volume reduction surgery for diffuse emphysema. Cochrane Database Syst Rev 2016;10:CD001001.
15. Tutic M, Lardinois D, Imfeld S, et al. Lung-volume reduction surgery as an alternative or bridging procedure to lung transplantation. Ann Thorac Surg 2006;82:208-13; discussion 213.
16. Anderson MB, Kriett JM, Kapelanski DP, et al. Volume reduction surgery in the native lung after single lung transplantation for emphysema. J Heart Lung Transplant 1997;16:752-7.
17. Criner GJ, Cordova F, Sternberg AL, et al. The National Emphysema Treatment Trial (NETT) Part II: Lessons learned about lung volume reduction surgery. Am J Respir Crit Care Med 2011;184:881-93.
18. ; Fishman A, Fessler H, et al. Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med 2001;345:1075-83.
19. Rathinam S, Oey I, Steiner M, et al. The role of the emphysema multidisciplinary team in a successful lung volume reduction surgery programme†. Eur J Cardiothorac Surg 2014;46:1021-6; discussion 1026.
20. Sabanathan S, Richardson J, Pieri-Davies S. Bronchoscopic lung volume reduction. J Cardiovasc Surg (Torino) 2003;44:101-8.
21. Snell GI, Peacock M, Garrett J. Lung volume reduction surgery: the Thoracic Society of Australia and New Zealand. Intern Med J 2001;31:112-5.
22. Snell GI, Holsworth L, Borrill ZL, et al. The potential for bronchoscopic lung volume reduction using bronchial prostheses: a pilot study. Chest 2003;124:1073-80.
23. Toma TP, Hopkinson NS, Hillier J, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 2003;361:931-3.
24. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-44.
25. Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet 2015;386:1066-73.
26. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med 2015;373:2325-35.
27. Valipour A, Slebos DJ, Herth F, et al. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. Am J Respir Crit Care Med 2016;194:1073-82.
28. Kemp SV, Slebos DJ, Kirk A, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial

Valve Treatment in Heterogeneous Emphysema (TRANSFORM). Am J Respir Crit Care Med 2017;196:1535-43.
29. Criner GJ, Sue R, Wright S, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). Am J Respir Crit Care Med 2018;198:1151-64.
30. 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. Respiration 2019;97:416-27.
31. Criner GJ, Delage A, Voelker K, et al. Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE). A Multicenter, Open-Label Randomized Controlled Clinical Trial. Am J Respir Crit Care Med 2019;200:1354-62.
32. Buttery SC, Lewis A, Latimer L, et al. Comparative Effect of Lung volume reduction surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement: the CELEB trial. Eur Respir J 2022;60:4567.s
33. Buttery SC, Banya W, Bilancia R, et al. Lung volume reduction surgery versus endobronchial valves: a randomised controlled trial. Eur Respir J 2023;61:2202063.
34. Kemp SV, Carby M, Cetti EJ, et al. A potential role for endobronchial valves in patients with lung transplant. J Heart Lung Transplant 2010;29:1310-2.
35. Perch M, Riise GC, Hogarth K, et al. Endoscopic treatment of native lung hyperinflation using endobronchial valves in single-lung transplant patients: a multinational experience. Clin Respir J 2015;9:104-10.
36. Klooster K, Ten Hacken NH, Slebos DJ. The lung volume reduction coil for the treatment of emphysema: a new therapy in development. Expert Rev Med Devices 2014;11:481-9.
37. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. Lancet Respir Med 2013;1:233-40.
38. 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;315:175-84.
39. 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 2016;315:2178-89.
40. Gompelmann D, Shah PL, Valipour A, et al. Bronchoscopic Thermal Vapor Ablation: Best Practice Recommendations from an Expert Panel on Endoscopic Lung Volume Reduction. Respiration 2018;95:392-400.
41. Snell G, Herth FJ, Hopkins P, et al. Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous emphysema. Eur Respir J 2012;39:1326-33.
42. Gompelmann D, Heussel CP, Eberhardt R, et al. Efficacy of bronchoscopic thermal vapor ablation and lobar fissure completeness in patients with heterogeneous emphysema. Respiration 2012;83:400-6.
43. Shah PL, Gompelmann D, Valipour A, et al. Thermal vapour ablation to reduce segmental volume in patients with severe emphysema: STEP-UP 12 month results. Lancet Respir Med 2016;4:e44-5.
44. Steinfort DP, Christie M, Antippa P, et al. Bronchoscopic Thermal Vapour Ablation for Localized Cancer Lesions of the Lung: A Clinical Feasibility Treat-and-Resect Study. Respiration 2021;100:432-42.
45. Criner GJ, Pinto-Plata V, Strange C, et al. Biologic lung volume reduction in advanced upper lobe emphysema: phase 2 results. Am J Respir Crit Care Med 2009;179:791-8.
46. Herth FJ, Gompelmann D, Stanzel F, et al. Treatment of advanced emphysema with emphysematous lung sealant (AeriSeal®). Respiration 2011;82:36-45.
47. Come CE, Kramer MR, Dransfield MT, et al. A randomised trial of lung sealant versus medical therapy for advanced emphysema. Eur Respir J 2015;46:651-62.
48. Fissure Closure With the AeriSeal System for CONVERTing Collateral Ventilation Status (CONVERT). 2023. NCT04559464. Accessed 11/09/2023.
49. Bezzi M, Levi G, Darwiche K, et al. CONVERT Trial: Collateral ventilation conversion by closure of fissure defect with AeriSeal Foam for BLVR with Zephyr valves. Eur Respir J 2022;60:1231.
50. Lee HJ, Shojaee S, Sterman DH. Endoscopic lung volume reduction. An American perspective. Ann Am Thorac Soc 2013;10:667-79.
51. Cardoso PF, Snell GI, Hopkins P, et al. Clinical application of airway bypass with paclitaxel-eluting stents: early results. J Thorac Cardiovasc Surg 2007;134:974-81.
52. Shah PL, Slebos DJ, Cardoso PF, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. Lancet 2011;378:997-1005.
53. DeCamp MM Jr, Lipson D, Krasna M, et al. The evaluation and preparation of the patient for lung volume

reduction surgery. Proc Am Thorac Soc 2008;5:427-31.
54. Fernandez-Bussy S, VanderLaan P, Ing A, et al. Histopathologic Results Post Bronchial Rheoplasty. D94. COPD: EPIDEMIOLOGY AND THERAPY. Am J Respir Crit Care Med 2019;199:A7043.
55. Valipour A, Fernandez-Bussy S, Ing AJ, et al. Bronchial Rheoplasty for Treatment of Chronic Bronchitis. Twelve-Month Results from a Multicenter Clinical Trial. Am J Respir Crit Care Med 2020;202:681-9.
56. Krimsky WS, Broussard JN, Sarkar SA, et al. Bronchoscopic spray cryotherapy: assessment of safety and depth of airway injury. J Thorac Cardiovasc Surg 2010;139:781-2.
57. Slebos DJ, Breen D, Coad J, et al. Safety and Histological Effect of Liquid Nitrogen Metered Spray Cryotherapy in the Lung. Am J Respir Crit Care Med 2017;196:1351-2.
58. Garner JL, Shaipanich T, Hartman JE, et al. A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD. Eur Respir J 2020;56:2000556.
59. Slebos DJ, Klooster K, Koegelenberg CF, et al. Targeted lung denervation for moderate to severe COPD: a pilot study. Thorax 2015;70:411-9.
60. Kistemaker LE, Slebos DJ, Meurs H, et al. Anti-inflammatory effects of targeted lung denervation in patients with COPD. Eur Respir J 2015;46:1489-92.
61. Koegelenberg CF, Theron J, Slebos DJ, et al. Antimuscarinic Bronchodilator Response Retained after Bronchoscopic Vagal Denervation in Chronic Obstructive Pulmonary Disease Patients. Respiration 2016;92:58-60.
62. Valipour A, Asadi S, Pison C, et al. Long-term safety of bilateral targeted lung denervation in patients with COPD. Int J Chron Obstruct Pulmon Dis 2018;13:2163-72.
63. Valipour A, Shah PL, Pison C, et al. Safety and Dose Study of Targeted Lung Denervation in Moderate/Severe COPD Patients. Respiration 2019;98:329-39.
64. Slebos DJ, Shah PL, Herth FJF, et al. Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW). A Multicenter Randomized Controlled Clinical Trial. Am J Respir Crit Care Med 2019;200:1477-86.

doi: 10.21037/amj-23-100
Cite this article as: Saeed H, Dibardino DM, Ma KC. Bronchoscopic treatments of chronic obstructive pulmonary disease (COPD): a narrative review. AME Med J 2024;9:18.