# Future Treatment of Emphysema with Roles for Valves, Novel Strategies and Lung Volume Reduction Surgery

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**KEYWORDS**

• Emphysema • Lung volume reduction • Bronchoscopic intervention

**KEY POINTS**

- Endobronchial valves are the main non-surgical intervention available to address the symptoms of emphysema.
- Multiple alternative strategies have been devised but have failed to achieve the reliable benefits seen with valves.
- Meticulous patient selection and transparent education of risks and benefits will allow the best allocation of surgery and non-surgical alternatives.

Previous articles in this issue chronicle the evolution of surgical attempts to improve lung function and to enhance the quality of life in emphysema patients by reducing the size of emphysematous lungs. The size reduction improves the air flow in the remaining lungs and enhances the matching of ventilation and pulmonary perfusion in the remaining lung tissue. The lineage of interventions actually began in the 1950s with the initial efforts of Otto Brantigan[1] and is punctuated by the pioneering resuscitation of the notion of volume reduction by Cooper and colleagues[2] in 1995.

Along the way, there have been some novel strategies with similar short-term (shrink the lungs) and long-term (improve lung function and reduce dyspnea) goals. Wakabayashi and colleagues reported in 1991 their efforts to treat emphysema by heating and shrinking lung tissue afflicted with bullous emphysema by applying a low-energy $CO_2$ laser to the surface of the diseased lung tissue. Their initial report[3] showed a nearly 10% mortality rate but also proved the underlying physiologic principle by demonstrating decreased total lung capacity (volume reduction) and the association with increased forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) demonstrated with pre- and postintervention testing.

Although there are multiple pharmacologic and nonpharmacological options to alleviate symptoms, none of these treatment modalities halts disease progression. The expanding disease burden has led to development of innovative therapeutic strategies that also aim to induce lung volume reduction over the past decades. Bronchoscopic lung volume reduction originated in 2001 and has continued to grow rapidly ever since. The previous articles in this issue have discussed lung volume reduction and the use of endobronchial valves for management of emphysema. This article discusses more recent developments in bronchoscopic and novel interventions and speculates on how these novel

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strategies may impact the future of lung reduction interventions.

## ENDOBRONCHIAL VALVES

This intervention is covered elsewhere in this issue but deserves brief mention here for the sake of completeness. This is the current mainstay of endoscopic options and therefore seems to be the most likely of any of these alternatives to surgery to be offered. In a recent review of the specialty on interventional pulmonology, Wahidi and colleagues[4] summarized the state of the art in all areas of this evolving subspecialty. Endobronchial valve therapy was the only modality mentioned among the multitude of endoscopic emphysema interventions. The physiologic and symptom improvements seen in trials tracking measured lung function, exercise tolerance, and self-reported quality of life were cited, as were the risks of procedural pneumothorax and uncertainty of the magnitude and duration of benefit for any individual. Valves are the current kingpin of nonsurgical interventions.

## LUNG VOLUME REDUCTION COILS

Nitinol coils are shape-memory devices that assume their preformed shape once bronchoscopically deployed into the subsegmental airways. Placed into an airway of some diseased and hyperexpanded lung, the device resumes the coiled shape and pulls the lung tissue into a compressed form, thus reducing the volume. Once they assume their initial and preferred shape, nitinol coils act by compressing the surrounding emphysematous lung parenchyma. In theory, this creates tissue tension and restores radial support to airways, thereby tethering nearby airways open to reduce airway collapse and air trapping during exhalation and exercise. These are nonobstructive devices, and they exert the desired effect immediately, unimpeded by the presence of any collateral ventilation. Since the first publication of endobronchial coil implantation by Herth and colleagues[5] in 2010, much has been published regarding the use of coils as a mode of bronchoscopic lung volume reduction.

Apart from improving the ventilatory mechanics of the affected emphysematous lung, lung reduction coils also potentially increase perfusion adjacent to the treated areas. In a quantitative analysis, Lador and colleagues[6] revealed that coil lung reduction resulted in a significant increase in perfusion to the coil-free areas immediately adjacent to the treated region, as well as in other ipsilateral untreated areas. This redistribution of pulmonary blood flow toward the better ventilated areas was presumed to be the result of better closure of vessels in diseased regions after coil placement, resulting in increased resistance to blood flow in the emphysematous lung and redirection to healthier regions of lower resistance. As a consequence, coil reduction may thus improve the pulmonary ventilation/perfusion ratio.

There have been 3 randomized controlled studies comparing coil lung reduction with medical therapy. The RENEW trial randomly assigned 315 emphysema patients to either a coil treatment group or to a standard medical care group.[7] At 1 year of follow-up, data showed a statistically significant improvement in the 6-min walk distance by 10.3 m with coil treatment ($P=.02$), along with median change in FEV1 by 7% ($P<.001$) and in the St. George's Respiratory Questionnaire with a shift of 8.9 points ($P<.001$), each difference favoring the coil group. The Réduction Volumique Endobronchique par Spirales (REVOLENS) study was a multicenter 1:1 randomized superiority trial comparing coil treatment with a usual care control group in 100 patients.[8] During the 1-year follow-up, authors demonstrated an improvement in exercise capacity with a significant decrease in lung hyperinflation and an associated improvement in self-reported quality of life. Subsequently, the 2 year prospective follow-up study showed sustained improvement in quality of life and a sustained decrease in pulmonary residual volume, with no late-onset events.[9] The longest follow-up study recently completed, the RESET study, showed a survival advantage at 5 years for endobronchial coil implantation in the subset of patients who had achieved a 10% reduction in residual volume (RV) at 3 months.[10] The ELEVATE study is a prospective, multicenter, randomized, controlled study that is currently being conducted to further identify disease characteristics using quantitative computed tomography (CT) scans to determine which patients will respond to coil treatment.[11]

In an attempt to compare outcomes across treatment modalities, Marchetti and colleagues[12] evaluated individuals who received bilateral coil therapy in previously reported trials and compared them with individuals who underwent lung volume reduction surgery (LVRS) within National Emphysema Treatment Trial. They demonstrated that placement of endobronchial coils in patients with advanced homogeneous emphysema reduced residual volume and total lung capacity, and increased walking distance compared with optimal medical therapy. Additionally, their study also showed improved walking distance and survival with coil use when compared with LVRS.

One of the most common complications reported after EBC is pneumonia or lower respiratory tract infections (20% incidence in the REVOLENS trial, 15% incidence in the RENEW trial). However, several of these pneumonias appeared to be noninfectious in nature and are considered by some experts to be secondary to the force of the coils on the lung tissue causing an inflammatory response. This response results in radiographic findings of dense consolidations that are unique to this treatment modality. These so-called coil-associated opacities (CAOs) are difficult to distinguish from pneumonia, and the clinical significance is unknown. Yet another potential drawback with these devices is that they are deemed permanent or at least very difficult to remove. Despite the concern and caveat of permanence, there are isolated reports of successful removal of coils even after 1 year postimplantation.[13]

An expert recommendation panel from 2017 summarized optimal criteria for coil implantation as follows: FEV1 less than 50%, RV less than 175%, RV/total lung capacity (TLC) less than 0.58, 6-minute walk distance 150 to 450 m.[14] They also emphasized on the importance of careful selection of patients, along with routine culture of bronchial secretions during the bronchoscopy procedure, thus addressing the concerns of a high risk for respiratory infections. Frequently, pharmacologic and nonpharmacological treatment need to be optimized before starting a coil treatment. This is crucial given the complexity, expense, and irreversibility of the treatment. Deployment of coils requires a multidisciplinary team approach with pulmonology, radiology, thoracic surgery, and pulmonary rehabilitation in selecting the most appropriate treatment for an individual patient.

## BRONCHOSCOPIC THERMAL VAPOR ABLATION

Bronchoscopic thermal vapor ablation is a fairly new treatment modality first described in 2009 as a novel way to reduce lung volume in the setting of emphysema.[15] The mechanism involves bronchoscopic instillation of heated water (at a temperature of 75°C) into the preselected target emphysematous segments. The resulting heat injury induces a local inflammatory reaction. Steam moves through air-containing spaces, and heat dissipation is related to tissue density, structure, and regional blood flow.[16] The inflammatory reaction promotes fibrosis and shrinkage of the targeted ventilated areas, leading to volume reduction of those poorly perfused lung segments. Because this therapy has no effect on the nontargeted lung tissue, bronchoscopic thermal vapor ablation can be used to manage intralobar heterogenous emphysema, with or without presence of collateral ventilation. Furthermore, it is currently the only mode of lung reduction intervention that leaves no implants in the patient.

The STEP-UP trial in 2016 was the first randomized trial comparing bronchoscopic thermal vapor ablation with standard medical treatment for emphysema.[17] In a 6-month follow-up report, results demonstrated a statistically significant 14.7% difference in FEV1 after bilateral thermal ablation compared with the control group, a 9.7-point reduction in St. George Respiratory Questionnaire (SGRQ), and a residual volume reduction of 302.5 mL.[18] Data obtained at the 12-month follow-up visits showed persistent improvements in FEV1 (9.2%) and SGRQ (8.4 points).

Ideal candidates for bronchoscopic thermal vapor ablation are identified using body plethysmography and CT scans. The favorable patients are characterized by severe hyperinflation (RV $\geq$175%) and upper lobe-predominant emphysema, with an FEV1 and diffusing capacity for carbon monoxide (DLCO) preferably at least 20% because of safety concerns. The targeted segments are identified as those with the highest disease severity, the highest heterogeneity index (HI), and the highest segmental volume.[19] Bronchoscopic thermal vapor ablation is a nonblocking, irreversible technique. The most common adverse events in the STEP-UP trial were chronic obstructive pulmonary disease (COPD) exacerbations and pneumonia/pneumonitis. Treatment of these complications relies on corticosteroids and antimicrobial therapy according to standard care. Clinical trials are underway to further study the benefits and risks with use of bronchoscopic thermal vapor ablation. Data gathered from such studies will enable continued improvement in patient selection and outcomes of vapor ablation over time.[20]

## ADDITIONAL NOVEL STRATEGIES

Targeted lung denervation is a novel potential therapeutic intervention for COPD. Using a bronchoscopically guided catheter-based lung denervation system (Holaira, Inc., Plymouth, Minnesota), radiofrequency energy is applied, and parasympathetic pulmonary nerves surrounding the main bronchi are ablated. This disrupts the autonomic input from the vagus nerve that has been shown to be elevated at baseline in COPD patients.[21,22] Consequently, the decreased bronchomotor tone results in bronchodilation and reduces airway hyperresponsiveness and mucus hypersecretion. The first in-human clinical trial by

Slebos and colleagues[23] in 2015 reported an increase of 11.6% in FEV1, an increase of 6.8 min in submaximal exercise cycle endurance, and a decrease of 11.1 points in SGRQ score. Further impacts of targeted lung denervation potentially include disruption of airway inflammatory mediators and airway remodeling.[24] Although it is not a volume reduction procedure and is not yet routinely used in clinical practice, targeted lung denervation may have synergistic effects when combined with other interventions and pharmacologic agents used for COPD management. Future studies are required to further evaluate its efficacy and safety profile.

Polymeric lung volume reduction involves bronchoscopic application of rapidly polymerizing biologic agents to reduce lung volume by blocking off the most emphysematous areas. Once applied, resorption atelectasis occurs from airway occlusion followed by subsequent airspace inflammation, and then remodeling. This remodeling occurs by way of scarring of lung parenchyma that provides a functional volume reduction. Clinical trials have studied the use of fibrin glue[25] and autologous blood patch,[26] with both showing promising results. The only randomized trial, the ASPIRE study published in 2015, demonstrated the intended positive effects but an unfavorable risk profile with this intervention.[27] The study was halted for business reasons after randomization of 95 out the planned 300 subjects. In this study, 44% of treated patients experienced adverse events requiring hospital admission and additional pharmacotherapy including steroids and antibiotics. The most frequent symptoms were pneumonia, COPD exacerbations, and respiratory failure. If adverse effects of this sort of treatment could be reduced or successfully mitigated, the cost-effectiveness and apparent ease of execution make this strategy an attractive intervention, and further research seems prudent. Currently, however, it appears that other forms of intervention are viewed as more favorable for additional development and testing.

Airway bypass was developed based on the observation that patients with severe emphysema had dilated terminal airway spaces and patent central bronchi, but collapsible midlevel airways that impeded exhalation. Creating a path from the dilated terminal airway to the patent central bronchus (airway bypass) could allow improved exhalation and reduce air trapping, lung distention, and dyspnea. To maintain patency of the bypass, stents were placed within the bypass channel with the aim of releasing trapped air from targeted areas. Paclitaxel-coated stents were used in varying numbers. Preliminary work demonstrated the proof of the principle; however, clinical studies failed to demonstrate significant functional outcomes.[28] Furthermore, there were long-term concerns for granulation tissue growth, stent occlusion, and stent migration, which occurred commonly. Further development of this novel intervention seems to be on hold.

## ONGOING CLINICAL TRIALS

A current trial is looking at lung volume reduction for severe emphysema by stereotactic ablative radiation therapy (ClinicalTrials.gov Identifier: NCT03673176). As commonly seen in stereotactic radiation therapy performed for lung cancer treatment, radiation typically leaves a scar in the area of lung that has been treated. This scarring process results in contraction of surrounding lung parenchyma that is essentially a focal example of lung volume reduction. There are existing data regarding lower risk of morbidity and mortality with stereotactic ablative radiotherapy (SABR) in lung cancer surgery, so it seems a clever pivot to see if the same attributes result in a favorable intervention for emphysema. One drawback is that the scarring process is associated with the density of tissue irradiated, and the most diseased portions of lung in emphysema have low density of tissue. It will be interesting to observe as trials unwrap the potential role of stereotactic radiation, a commonly available treatment that is applied with great precision, as a potential strategy for patients with emphysema but no cancer.

Various combinations of bronchoscopic lung reduction methods are also being evaluated. Lung Volume Reduction in Severe Emphysema Using Bronchoscopic Autologous Blood Instillation in Combination With Intra-bronchial Valves (BLOOD-VALVES) is one such pilot study. (ClinicalTrials.gov identifier: NCT03010449). It seems natural that other combination strategies of novel therapies might be considered in the future.

## FUTURE ROLE FOR LUNG REDUCTION INTERVENTIONS

Lung reduction in the broad sense is based on the principle that states that by removing diseased emphysematous lung tissue, one can improve symptoms, respiratory physiology, and possibly survival in a clearly identifiable subgroup of patients with advanced emphysema. Despite that accepted principle, with an estimated 3.8 million patients with emphysema in the United States, it is clear that only a miniscule proportion of these patients end up undergoing lung reduction of any kind. This potential treatment option for palliating

life that is based on sound clinical and physiologic principles may be underutilized.

One of the main reasons is the perception regarding the potential survival benefits and risks associated with the surgery. Studies evaluating LVRS may possibly have placed a strong emphasis on survival benefits without similar regard for the value of palliation. In a debilitating and progressive disease such as emphysema, however, palliation without lengthening of life span can be especially rewarding. An example might be the subgroup analyzed in the National Emphysema Treatment Trial (NETT), in which patients had upper lobe predominant emphysema and high exercise tolerance. Those patients did not receive a predictable survival advantage with lung volume reduction surgery, but they did receive a durable advantage in exercise tolerance, relief from respiratory symptoms, and patient-reported quality of life.

Furthermore, in NETT, patients were enrolled between 1998 and 2002. Since then, much progress has been made both in the surgical approach leading to broad adoption of minimally invasive approaches (VATS and robotic) in the surgery, and enhancements in postoperative care. Hence, this fairly rare operation has the potential to be revived with modern surgical technology, much as the original Brantigan operation was revived by Cooper after the passage of 4 decades of incremental improvements in imaging, medications, surgical technology, and perioperative care. In the same period of time, from 1998 to 2021, the authors have seen the expected and acceptable mortality of a lobectomy for lung cancer drop from 3% to 4% to less than 1%. It seems reasonable to think that the same could occur with surgical lung volume reduction.

Careful patient selection remains key, regardless of the technique or approach. This maxim goes back to the 1990s, when Cooper and colleagues released their first series of patients treated with LVRS. They emphasized from their experience that favorable outcomes from LVRS required careful selection of appropriate patients, and multidisciplinary team approach by pulmonologists, thoracic surgeons, and other relevant specialists. The same remains true today with other methods of reducing lung volume to address symptoms of emphysema. In the main result paper from the LIBERATE trial demonstrating efficacy for endobronchial valves, the authors described the fact that 909 patients were consented for evaluation and treatment, but only 160 patients met the full inclusion trial.[29] Just as with the early studies in surgical volume reduction, the sweet spot of appropriate hyperexpansion, location of disease, disease that is severe but not too severe, preserved functional reserve and acceptable comorbid conditions remain elusive challenges.

The challenge that lies ahead is to ensure that all lung volume reduction therapies are individualized, comprehensive, and patient-focused. This will require development of expert centers with multidisciplinary teams and availability of all treatment modalities and surgeon expertise for patient care and further development of lung volume reduction therapies. The notion of personalized medicine is increasingly emphasized in all aspects of the shared medical field and in some notable areas of thoracic surgery. The increased knowledge about targeted therapy, immunotherapy, and mutational analysis of lung cancer has been transformative. The current strategy for matching patients to specific drugs for adjuvant or definitive chemotherapy bears no resemblance to the strategy relied upon 10 years ago. It seems reasonable that the accumulated data from many surgical and bronchoscopic volume reduction clinical trials, in addition to data from administrative databases describing actual care provided in the modern era, could be mined to provide personalized expectations for outcomes for all interventions. This would allow better shared decision making for the patient and enhanced collaboration among the specialists to offer the appropriate intervention.

Transparency of outcomes has done much to improve patient selection and quality improvement processes throughout the surgical field. The knowledge that outcomes from a single institution or even a single practitioner might be available for comparison with outcomes from others has certainly altered behavior in the cardiothoracic surgical field. Surgical mortality used to be viewed as the inevitable risk associated with taking bold steps toward a positive outcome. Surgical databases and public reporting have certainly influenced risk tolerance and the broad consideration of multimodality treatment options. Ongoing monitoring and public reporting of the risk of death and complications, as well as the benefits derived from all of the interventions aimed at emphysema, would provide critical information to patients and those advising them. This type of information should be demanded by specialty insiders, disease advocacy groups, and payors.

New parameters for study have been created using clever utilization of existing technology and analytics that might better inform patient selection for volume reduction intervention. Analytical morphomics is a novel approach using semiautomated image processing to quantitate various aspects of body composition from standard preoperative CT scans. These are objective

measurements of physical properties that might be missed by the standard clinician view, but which are highly associated with outcomes when measured and analyzed systematically. For example, Lin and colleagues at the University of Michigan demonstrated that there are numerous, readily available, morphomic factors that are associated with physiologic reserve and frailty and could serve as independent predictors of survival, prolonged ventilation, and excessive length of stay after lung transplantation.[30] The authors suggested that routine use of morphomics preoperatively could improve recipient selection and risk stratification. If such as strategy could be useful for predicting outcomes in lung transplantation, it certainly could offer important insights when considering treatment options for lung volume reduction intervention.

It seems unlikely that any single modality will emerge as a dominant therapy in this highly nuanced field. However, with meticulous patient selection to identify and include those most likely to benefit and to identify and exclude those most likely to suffer treatment related complications, one can make the best case for specific intervention above and beyond best medical therapy. One size most assuredly does not fit all in this particular arena. One patient might agree to a 3% to 4% mortality risk in order to get a 25% to 40% increase in pulmonary function, whereas other patients might prefer a 1% mortality risk to achieve a 10% to 15% increase in pulmonary function. Additionally, optimal patient preparation with minimally invasive surgical intervention and expert perioperative recovery can provide the interventional boost intended by the chosen therapy while minimizing the potential associated complications.

## CLINICS CARE POINTS

- Lung volume reductions ought to be individualized and patient focused, and require a multi-disciplinary team approach comprising experts in surgical and non-surgical treatments.
- Careful patient selection is key in determining a favorable response to the selected treatment modality.
- Certain interventions described in this chapter, such as endobronchial coils and bronchoscopic thermal vapor ablation are irreversible and hence careful discussion and planning is critical prior to their application.
- Pharmacological and non-pharmacological treatment of emphysema should be optimized prior to any surgical or bronchoscopic intervention in order to prevent complications such as infections, pneumonias or coil-associated opacities.

## DISCLOSURES

The authors have no disclosures or conflicts of interest.

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