Global Initiative for Chronic Obstructive Lung Disease

2023 REPORT

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™

Excerpted from Chapter 3 of the GOLD Report (pages 82-87):
Interventional & Surgical Therapies for COPD
The full 2023 GOLD Report can be accessed at goldcopd.org/2023-gold-report-2/

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

INTERVENTIONAL & SURGICAL THERAPIES FOR COPD

COPD is associated with airway and lung parenchyma structural changes that provide potential targets for interventional and surgical treatments to alleviate dyspnea, reduce cough and mucous production, and improve quality of life (**Figure 3.2**).

Overview of Current and Proposed Surgical and Bronchoscopic Interventions for People with COPD — Figure 3.2

Symptoms	Chronic Mucus Production	Exacerbations	Dyspnea
Disorders	• Chronic bronchitis	• Acute and chronic bronchitis • Bulla • Emphysema • Tracheobronchomalcia	• Bulla • Emphysema • Tracheobronchomalcia
Surgical and Bronchoscopic Interventions	• Nitrogen cryospray • Rheoplasty	• Targeted lung denervation	• Giant bullectomy • Large airway stenting • EBV • Coil • Thermal vapor ablation • Lung sealants • LVRS • Lung transplantation

Lung structural related therapies for COPD include airway and emphysematous predominant treatments. Phenotyping patients with clinical, physiological, and imaging tests is critical to select appropriate candidates and in assessing the benefits, timing, and type of intervention to be performed. Multidisciplinary collaboration of pulmonology, thoracic surgery and imaging disciplines are necessary to ensure quality outcomes.

Airway predominant treatments are currently the subject of Phase III clinical trials; emphysematous based treatments include bullectomy, lung volume reduction surgery, bronchoscopic lung reduction and in select cases, lung transplantation. Each of these therapies are reviewed below.

Surgical and interventional treatments for patients with emphysema depends upon the severity of patient symptoms despite optimized medical treatment, the specific structural abnormalities and features of the lung seen on CT imaging, the presence of pulmonary and non-pulmonary comorbid conditions, physiological assessment, and the balance of benefits and risks for the individual patient.

Lung surgical treatments for patients with emphysema

Bullectomy

Giant bullectomy is a rare, but effective procedure for surgical resection of bulla that occupies > one-third of a hemithorax and compresses adjacent viable lung tissue. Reductions in dyspnea, and improvements in lung, respiratory muscle, and cardiac performance, as well as exercise tolerance have been reported. [(458-460)] Blood or thrombin instillation may be effective in those unfit for resection.[(461-463)]

Lung volume reduction surgery (LVRS)

Lung hyperinflation is a major contributor to impaired respiratory function and is associated with increased hospitalization and mortality. Hyperinflation increases the sensation of breathlessness and causes a reduction in exercise due to increased chest wall elastance and reduced respiratory muscle and cardiac mechanics. Hyperinflation is most pronounced in those patients with COPD that have an emphysematous predominant phenotype.

With LVRS, the most emphysematous portions of the lungs are resected to reduce hyperinflation,[(464)] and increase lung elastic recoil pressure and density.[(465)] The structural changes that result from LVRS can significantly improve expiratory flow and chest wall, respiratory muscle and cardiac mechanics.[(466,467)] that results in improvements in FEV1, walking distance and quality of life.[(468-471)] LVRS can be performed unilaterally or bilaterally. In the National Emphysema Treatment Trial (NETT), a RCT that included severe emphysema patients, bilateral LVRS improved survival in patients with upper-lobe emphysema and low post-rehabilitation exercise capacity.[(246)] In similar patients with high post-pulmonary rehabilitation exercise capacity, no difference in survival was noted after LVRS, although health status and exercise capacity improved. A reinterpretation of the NETT data at 5 years post treatment showed sustained improvements in lung function, exercise, shortness of breath and quality of life.[(472)]

LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with FEV1 ≤ 20% predicted and either homogeneous emphysema on high resolution computed tomography or a DLco ≤ 20% of predicted.[(473)] In addition to a lower DLco, a lower FEV1 and BMI have also been reported to increase mortality.[(474)] Postoperative BODE (body mass index, degree of airflow obstruction, level of dyspnea and exercise capacity) is a predictor of survival following LVRS.[(475)] Successful outcomes with LVRS have been reported in select patients with severely impaired DLco when hyperinflation is severe, and associated with approachable emphysematous targets for resection.[(476)] Identification of target zones using three-dimensional computed tomographic imaging is beneficial in selecting resectable target zones. [(477)] A prospective economic analysis in NETT indicated that LVRS is costly relative to healthcare programs that do not include surgery.[(478)]

Post NETT, experienced centers have reported substantial physiological and functional improvements with LVRS with reduced morbidity and mortality.[479,480] However, the numbers of patients undergoing LVRS remains low worldwide.[480,481] Several patient factors such as difficulty in obtaining referrals, the perception of increased surgical complications, and limited continuity of care are reasons why the numbers of patients undergoing LVRS remain low despite its reported benefits.[482] Additionally, respiratory physicians are reluctant to refer patients for LVRS because of the uncertainty about the associated complications, or lack of access to a multidisciplinary team to discuss patient candidates.[483] To achieve successful outcomes, a multidisciplinary team is key to select potential LVRS patients and coordinate postoperative care.[484]

Lung transplantation

Over 1,000 patients with COPD undergo lung transplantation on an annual basis, about 30.6% of all patients that undergo transplantation.[485] Since implementation of the lung allocation severity (LAS) scoring system, the numbers of patients undergoing lung transplantation for COPD is exceeded by the numbers of patients receiving transplantation for interstitial lung diseases. Patients with COPD should be referred for consideration of lung transplantation when they have progressive disease despite maximal medical treatment, are not candidates for lung volume reduction surgery, have a BODE index of 5 to 6, a $PaCO_2$ > 50 mmHg (6.6 kPa) and/or PaO_2 < 60 mmHg (8 kPa) and FEV1 < 25%.[486] They should be considered for listing for lung transplantation when the BODE index is > 7, FEV1 is < 15 to 20%, and they have had three or more severe exacerbations during the previous year, one severe exacerbation with hypercapnic respiratory failure, or have moderate to severe pulmonary hypertension.[486] In the last decade, lung transplant has been increasingly performed in patients of older age, higher BMI, prior chest surgery, poor nutritional status, prior evidence of chronic infection, cardiovascular disease, or extrapulmonary comorbid conditions.[487]

Lung transplantation in patients with COPD has been predominately associated with an improvement in quality of life, not an increase in survival except for COPD patients with severe AATD or those severely impaired with high BODE scores.[458,488-494] The median survival post lung transplantation for COPD is 5.9 years.[485] Over 70% of lung transplants conducted in COPD patients are double lung transplants; the remainder are single lung transplants.[495] Bilateral lung transplantation leads to longer survival in patients with COPD especially in those < 60 years of age.[496,497]

Two unique native lung complications have been proposed to account for the superiority of double lung transplantation in patients with COPD, native lung hyperinflation and lung cancer occurrence in the native lung.[498,499] Lung cancer has been reported to occur in the native lung following single lung transplantation with an incidence of 5.2-6.1%.[498,500] Native lung hyperinflation following single lung transplantation for COPD has been reported to occur 15-30% of the time.[501,502] Positive pressure ventilation in a patient with COPD with an overly compliant native lung coupled with reduced compliance in an edematous allograft may result in native lung hyperinflation. However, some studies have shown no impact of single lung transplant on post-transplant morbidity, and even improved survival following single lung transplantation in patients with COPD.[501,503,504]

In general, lung transplantation has limited availability due to the shortage of donor organs and cost, thus single vs. double lung transplantation is balanced between individual patient factors vs. societal demands to increase the donor pool for eligible recipients.[505] The complications most seen in COPD patients after lung transplantation are acute rejection, bronchiolitis obliterans, opportunistic infections and lymphoproliferative disease.[506]

Bronchoscopic interventions in COPD

Bronchoscopic Interventions to reduce hyperinflation in severe emphysema

Due to the morbidity and mortality associated with LVRS, less invasive bronchoscopic approaches to lung reduction have been examined.[507] These include a variety of different bronchoscopic procedures to perform lung volume reduction (i.e., endoscopic lung volume reduction, ELVR) including airway bypass stents, endobronchial one-way valves (EBV) , self-activating coils, sealants and thermal ablative techniques.[507] Bronchoscopic techniques depend upon the presence of an intact fissure between the treated and non-treated lobe for EBV to be successful, but not for the other techniques. Although these techniques differ markedly from one another they are similar in their objective to decrease thoracic volume to improve lung, chest wall and respiratory muscle mechanics.

Endobronchial one-way valves (EBV)

EBV are the most well studied therapy of all the ELVR techniques. RCTs showed significant increases in FEV1 and 6-minute walk distance as well as health status in subjects selected for the absence of interlobar collateral ventilation compared to the control group at 6 and 12 months.(508,509) Adverse effects in the endobronchial valve treatment group in both studies included pneumothorax, valve removal or valve replacement.(508) Pneumothorax was seen in 26.6% of subjects treated with the endobronchial valve usually within the first 72 hours of the procedure (76%).(509-511) But benefits have also been shown in patients with heterogeneous compared to those with homogenous emphysema in one study.(508)

Early-onset pneumothorax in the EBV treated group likely results from lung structural changes due to acute volume reduction in the emphysematous targeted lobe by valve therapy that triggers rapid ipsilateral non-targeted lobe expansion, a recognized indicator of successful target lobe occlusion in patients with intact fissures or absence of collateral ventilation.(512) Pleural adhesions may also be a contributing factor to the development of a pneumothorax.(513) The occurrence of pneumothorax highlights the need for physicians performing this procedure to have expertise in the management of procedural complications.(512)

After the post-procedural period however, patients treated with EBV compared to usual care tend to have a lower number of exacerbations and episodes of respiratory failure. A comparison of treatment benefits and complications associated with EBV compared to LVRS show comparable benefits with endobronchial valve treatment but with fewer complications.(509) Additionally, ELVR has similar beneficial effects whether it is performed in the upper or lower lobes.(509,512)

Improved survival has been associated with post procedural atelectasis of the treated lobe post EBV.(514-516) Improved survival has also been reported in patients with severe hyperinflation undergoing EBV compared to a matched population not undergoing ELVR.(517)

When preferences for medical treatment for patients with severe emphysema are elicited, the majority chose treatments with EBV over LVRS or continued medial therapy.(518) ELVR with EBV is clinically available and approved for treatment in many countries in the treatment of patients who have intact fissures or lack collateral ventilation.(509,519,520)

The following bronchoscopic lung volume reduction techniques do not depend upon the presence of intact fissures or absence of collateral ventilation.

Airway bypass stents

Airway bypass stents are transbronchial passages that are created through the walls of the central airways into the emphysematous parenchyma to facilitate the emptying of trapped gas. In a prospective randomized controlled clinical trial, patients had short term improvements, but no durable improvements were found in lung function, 6 MWD or quality of life.(521)

Sealants

A multicenter study examining the effects of a lung sealant to create lung reduction was discontinued prematurely; while the study reported significant benefits in some physiologic parameters, the intervention was associated with significant morbidity and mortality.(522)

Vapor ablation

In a prospective RCT, targeted thermal vapour ablation of more diseased emphysematous segments to produce fibrosis and atelectasis resulted in clinically meaningful and statistically significant improvements in lung function and health status at 6 months. COPD exacerbation was the most common serious adverse event. Durability of these changes was subsequently reported at 12 months follow-up.[523,524] This therapy has limited clinical availability.

Self-activating coils

Multicenter trials have examined nitinol coils implanted into the lung compared to usual care on changes in 6-minute walk distance, lung function and health status in patients with advanced homogenous and heterogeneous emphysema. Studies reported an increase in 6-minute walk distance with coil treatment compared to control and smaller improvements in FEV1, and quality of life measured by St George's Respiratory Questionnaire.[525-527] Patients with baseline residual volume > 200% predicted, emphysema score > 20% low attenuation area, and absence of airway disease are more likely to have clinically meaningful improvements in lung function and quality of life.[528]

Major complications included pneumonia, pneumothorax, hemoptysis and COPD exacerbations occurring more frequently in the coil group.[526] This therapy has limited clinical availability.

Additional data are needed to define the optimal bronchoscopic lung volume technique to produce bronchoscopic lung volume reduction in patients who lack fissure integrity, or exhibit collateral ventilation, and to refine the procedure to reduce complications and improve longer term clinical outcomes.[526]

Sequential performance of LVRS or ELVR prior to or following lung transplantation

Because COPD is a progressive disease, LVRS or ELVR may be followed by lung transplantation. Conversely, patients who undergo single lung transplantation may subsequently undergo LVRS or ELVR to treat the hyperinflated native lung. In hyperinflated patients with advanced emphysema, LVRS or ELVR might be effective treatments to either delay the need for lung transplantation or optimize the condition of patients who may eventually require lung transplantation.[529-531] In some patients following single lung transplantation, the performance of LVRS or ELVR to decrease native lung hyperinflation may improve lung function and performance status.[532-537] The incidence of postoperative bleeding requiring re-exploration and renal dysfunction requiring dialysis or the use of extracorporeal membrane oxygenation (ECMO) may be higher in patients undergoing lung transplantation following LVRS.[538,539] Previous ELVR has been reported to have no impact on morbidity or survival post subsequent lung transplantation but may affect microbial colonization.[539,540]

Airway predominant treatments

Abnormalities that predominantly involve the airways, such as excessive dynamic collapse of the large airways (tracheobronchomalacia) chronic bronchitis and frequent and severe exacerbations not responsive to optimal medical treatment pose significant clinical challenges.

Excessive dynamic airway collapse (EDAC)

EDAC or tracheobronchomalacia (TBM) is a disorder of the large airways where abnormal collapsibility occurs with expiration. Commons symptoms are dyspnea, cough and wheezing with inability to expectorate phlegm. In a cross-sectional analysis of smokers the presence of excessive dynamic airway collapse observed on CT imaging was 5% and associated with worsened quality of life and more frequent and severe exacerbations.[541] Airway stenting and tracheoplasty may be beneficial in select patients.[542,543]

Chronic bronchitis is a common and significant contributor to a worsening of patient's symptoms of cough and sputum production and cause worsened quality of life and increased mortality. No specific medical intervention significantly and consistently alleviates chronic bronchitis. Newer interventions have been proposed to reduce mucous hypersecretion by eliminating airway goblet cell hyperplasia and submucosal glands.

Nitrogen cryospray

Liquid nitrogen metered cryospray is delivered to the central airways and ablates the epithelium to a depth of 0.1 to 0.5 mm.[348] After treatment, rapid regeneration of normal epithelium occurs without scarring and may potentially treat chronic bronchitis.[544]

Another novel treatment for chronic bronchitis is rheoplasty.[545] Rheoplasty delivers short bursts of high frequency electrical energy to the airway epithelium targeting submucosal tissues and goblet cells to facilitate their replacement with healthier tissue. Ongoing phase III randomized clinical trials are evaluating the efficacy of these therapies.[546,547]

Lung denervation

Targeted lung denervation is another therapy currently undergoing phase III clinical trial study to determine its impact of frequent moderate or severe exacerbations in patients with COPD already on maximal inhaled respiratory treatment.[548,549] The therapy intends to disrupt the parasympathetic nerve transmission to and from the lungs. In patients with COPD, basal parasympathetic tone is elevated and increases acetylcholine levels and mucus production and airway contraction. The treatment uses a water-cooled catheter with radiofrequency energy to disrupt parasympathetic nerve transmission while protecting the airway surface.[350,351,549,550]

Key points for interventional therapy in stable COPD are summarized in **Table 3.11**.

Interventional Therapy in Stable COPD

Table 3.11

Lung Volume Reduction Surgery	• Lung volume reduction surgery improves survival in severe emphysema patients with an upper-lobe emphysema and low post-rehabilitation exercise capacity **(Evidence A)**
Bullectomy	• In selected patients, bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance **(Evidence C)**
Transplantation	• In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Evidence C)**
Bronchoscopic Interventions	• In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)**
Bronchoscopic Interventions Under Study	• Phase III trials are currently being conducted to determine the efficacy of treatments for patients with refractory exacerbations and chronic bronchitis using cryospray, rheoplasty and targeted lung denervation technology

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