REVIEW ARTICLE

Chronic Obstructive Pulmonary Disease: Part IV A Review of Surgical Managements of Chronic Obstructive Pulmonary Disease

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Abstract

Medical and non-pharmacological treatments continue to be the initial managements for chronic obstructive pulmonary disease (COPD). These managements have evolved over time, but given the high mortality and morbidity of COPD, much work still needs to be done. To date, none of the existing pharmacological therapies for COPD has been shown conclusively to modify the long-term decline in lung function. Several trials have been completed to evaluate options that can improve patient symptoms and quality of life. Optimal management for patients with COPD requires both pharmacologic and non-pharmacologic managements. To date, the only treatments that can modify the course of COPD and potentially cure the disease are surgical treatments. Some of the surgical managements we discussed in this review include Lung Volume Reduction Surgeries (LVRS), Bronchoscopic Volume Reduction Surgery (BVRS), bullectomy and lung transplants. The indications for these surgical managements have also been discussed in this article. Patients for surgical managements have to be appropriately selected to avoid some of the major adverse events that can occur because of some of the treatment modality.

Keywords: Lung Volume Reduction Surgeries, Bronchoscopic Volume Reduction Surgery (BVRS), bullectomy and lung transplants.

Introduction

Surgical management is the only known curative treatments for COPD.

The main surgical options used for the treatment of COPD are lung volume reduction surgery (LVRS), Bronchoscopic Volume Reduction Surgery (BVRS), bullectomy, and lung transplantation. Unfortunately, most patients with COPD are not surgical candidates. In order for a COPD patient to undergo any surgical procedure, they have to be carefully selected and must meet the criteria for surgical intervention for the benefits of the surgery to outweigh the harm. These procedures are reserved only for patients who remain symptomatic despite optimal medical treatment. In fact most patients considered for surgery are symptomatic with shortness of breath, pain, or spontaneous pneumothorax.[1] Lung coil or vapor ablation therapies could be considered along with LVRS. Traditionally, Patients with homogenous emphysema are not routinely considered candidates for LVRS; however, bronchoscopic lung reduction has been successful especially when endobronchial valve, vapor ablation or coil therapies are used. [2]

Lung transplant is also a major surgical treatment option for patients with COPD who are not candidates for endoscopic or surgical lung volume reduction. Referral criteria for lung transplantation include COPD with progressive disease, BODE index of 5 to 6, Pco2 > 50 mmHg or 6.6 kPa and/or Pao2 < 60 mmHg or 8.0 kPa, and FEV1 < 25% predicted. [3]

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) also known as reduction pneumoplasty, is a surgical intervention that consist of reducing lung volume by wedge excision of emphysematous tissue. It is a surgical intervention that could be beneficial and preferred in some patients with poorly controlled advanced emphysema despite optimal medical therapy. LVRS is a treatment option in selected COPD patients with emphysema. LVRS could be bilateral or unilateral. It improves breathing mechanics as well as lung function.[4] Diaphragm length, trans-diaphragmatic pressures, lung recoil and reduce ventilatory drive also improve after LVRS, resulting in improvements in exercise capacity, dyspnea, general health, and quality of life.[5,6,7-9] Significant improvement was also noted in the quality of sleep and neurobehavioral functioning.[10-13]

Fishman et al. conducted a randomized trial on 1,218 patients comparing lung-volume-

reduction surgery with medical therapy for severe emphysema. They found out that lung-volume-reduction surgery increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy. Secondly, LVRS yields a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity. Patients for LVRS must be appropriately selected in order to reap any benefits from the surgery. Patients who were previously reported to be at high risk or have a high base-line exercise capacity or non-upper-lobe emphysema were found to have increased mortality and negligible functional gain.[14]

LVRS reduces the size of mismatching between the hyper-inflated lungs and the chest cavity, causing an increase in elastic recoil and an improvement in expiratory airflow.[14-18] This causes the diaphragm to return to a more normal curved and lengthened configuration.[19,20] Secondly with the reduction of lung volumes there is also a reduction in dynamic hyperinflation during physical exercise leading to an improvement exertional dyspnea.[9] LVRS decreases intrathoracic pressures leading to an improvement in left ventricular filling, end-diastolic dimension, and cardiac index.[21] Clarenbach et al. conducted a randomized controlled trial in 30 patients with severe COPD and emphysema scheduled for LVRS and found out that endothelial function and blood pressure improved 3 months after LVRS in these patients.[4] The six-minute-walk distance increases from an average of 1,239 to 1,286 feet 6 a month.[10] After LVRS, FEV1 increases from about 28.1% predicted to 36.2%. The improvement is greatest at 6 months.[10]

Prior to performing LVRS, pulmonary function tests, a six-minute walk test, arterial blood gas, electrocardiogram, echocardiogram with measurement of pulmonary artery pressures, a cardiopulmonary exercise test, and high resolution computed tomography (HRCT) have to be completed. These tests will aid in determining the most appropriate patients for LVRS based on the indications noted on **table 1,** and may also aid in the differential diagnosis of shortness of breath.

Table 1: Indications for LVRS

Indications for unilateral LVRS. (119)

- unilateral asymmetric emphysema
- severely asymmetric emphysema
- contralateral pleurodesis
- contralateral thoracotomy
- hemodynamic instability
- massive air leak during the first side of a planned bilateral LVRS
- severe native lung hyperinflation after single lung transplantation for emphysema

Indications for bilateral LVRS. (110,120,121,122)

- Age <75 years
- Ex-smoker (4-6 months)
- Clinical picture consistent with emphysema
- Disability despite maximal medical therapy and pulmonary rehabilitation
- Absence of clinically significant bronchiectasis and absence of high daily production of sputum
- FEV1 after bronchodilator <45 percent predicted
- Hyperinflation (TLC >100 percent predicted, RV >150 percent)
- Post rehabilitation 6-minute walk distance >140 meters
- Low post rehabilitation maximal achieved cycle
- Chest radiograph - hyperinflation
- HRCT confirming severe emphysema
- Upper lobe predominant emphysema
- Six minute walk distance >140m

FEV1: forced expiratory volume in one second, TLC: total lung capacity; RV: residual volume, PaO2: arterial partial pressure of oxygen; PaCO2: arterial partial pressure of carbon dioxide; HRCT: high resolution computed tomography

Other than the indications to LVRS noted on **table 1,** LVRS can also per performed as a bridge to transplantation. Unilateral LVRS can be performed early post-transplant to treat acute native lung hyper expansion or late to treat chronic native lung hyperexpansion. In addition, unilateral LVRS can be performed simultaneous with single lung transplantation to prevent native lung hyper expansion.

Table 2: Contraindications for LVRS

Contraindications to LVRS [14,22,23]
• Age ≥75 years
• Active tobacco use
• Life expectancy <2years
• Severe obesity BMI>31.1 in men and 32.2 in women or cachexia.
• Previous thoracic procedure such as pleurodesis.
• Surgical constraints like chest wall deformity
• Pulmonary hypertension (PA systolic >45 mmHg, PA mean >35 mmHg)
• Clinically significant bronchiectasis
• Coronary heart disease
• Heart failure with low ejection fraction
• Giant bulla taking up more than 30% of the ling in which it is located
• Oxygen requirement of >60 per min to maintain saturations of 90% or above
• Extensive pleural symphysis from pleural disease or previous chest surgery
• Daily use of prednisone>
• Uncontrolled hypertension
• Forced expiratory volume in one second (FEV1) ≤20 percent predicted with either DLCO ≤20 percent predicted or homogeneous emphysema
• PaO2 ≤45 mmHg on room air
• PaCO2 ≥60 mmHg
• Homogeneous emphysema with FEV1 ≤20 percent predicted
• Significant pleural or interstitial changes on HRCT
• Non-upper lobe predominant emphysema
• High post rehabilitation maximal achieved cycle

LVRS is substantially more expensive than medical therapy. In an updated analysis to the Nett study, Ramsey SD et al. reported the cost-effectiveness of LVRS versus medical therapy of USD $140,000 per quality-adjusted life-year (QALY) gained (95% CI, $40,155 to $239,359) at 5 years, and projected to be $54,000 per QALY gained at 10 years. In subgroup analysis, the cost-effectiveness of LVRS in patients with upper-lobe emphysema and low exercise capacity was $77,000 per QALY gained at 5 years, and projected to be $48,000 per QALY at 10 years.[124] Postoperative in-hospital stay after LVRS is about 10 days. Survival after LVRS is

approximating 90% at 1 year, 77% at 3 years, and 65% at 5 years. Patients with upper lobe–predominant disease have a relatively better outcome.[10,14]

Major short-term complications of LVRS include: persistent air leaks and mechanical ventilation for more than two days, pneumonia, arrhythmias, reintubation and death.

Mortality after LVRS at three months[10]

- Respiratory cause in 43%
- Cardiovascular cause in 18%
- Multisystem organ failure in 7%
- Cerebrovascular abnormalities in 4%
- Unclassified in 25%

Bronchoscopic Volume Reduction Surgery (BVRS)

Because of the poor out come from LVRS, less invasive approaches such as Bronchoscopic volume reduction surgery (BVRS) have been attempted. A variety of Bronchoscopic techniques have been attempted with variable results. The aim of all the methods of BVRS is to improve chest muscle mechanics.[24] Fissure integrity and lack of interlobar collateral ventilation are major determining factors in the use of specific bronchoscopic techniques. Endobronchial valve, lung coil treatment, vapor ablation therapy or LVRS could all be useful in patients with fissure integrity or lack of interlobar collateral ventilation based on physiologic assessment. [24] Vapor ablation, lung coil therapy or LVRS may be performed in patients with lack of fissure integrity or interlobar collateral ventilation but endobronchial valve therapy is not useful. Patients with heterogeneous upper lobe predominant emphysema may be candidates for either LVRS or bronchoscopic lung reduction approaches. Lung coil or vapor ablation therapies along with LVRS could be considered if interlobar collateral ventilation is present. The presence of interlobar collateral ventilation would exclude the use of endobronchial valve therapy. Patients with homogenous emphysema are not routinely considered candidates for LVRS, however BVRS can be successful using endobronchial valve, vapor ablation or coil therapies. The presence of interlobar collateral ventilation is important in selecting endobronchial valve as the intervention of choice.[24]

Bullectomy

A bulla is defined as an air space in the lung measuring more than one centimeter in diameter in the distended state. A giant bulla is one that occupies at least 30 percent of a hemithorax.[25-27] Bullectomy is the removal

of a large bulla that is decompressing the adjacent lung parenchyma and is not contributing to gas exchange. Prior to performing bullectomy on any patient, it is very important to estimate the effect of the bulla on the lung and the function of the remaining lung. In carefully selected patients, bullectomy can reduce shortness of breath and improve lung function.[28] Patients with a single bulla occupying at least half the volume of the pleural cavity would be considered candidates for surgery, while patients with smaller lesions and no symptoms would be more controversial.[1]

Bullectomy can be performed as a thoracoscopic procedure, but the technique of the operation is quite variable and depends on the anatomical details of the bulla as well as the preferred approach of the surgeon. Formal lobectomy seem to be a less attractive option to most surgeons.[1] Parenchymal air leaks are the biggest single postoperative complication and can generally be appropriately managed with options like buttressed stapled lines, pleural tent, pleurectomy, biological glues, or ambulatory Heimlich valves. All patients with emphysema seem to experience a progressive decline in FEV_1 over time, so patients with near normal underlying lung at the time of bullectomy will begin at a higher functional baseline than those with moderate or severe emphysema in the remaining lung.[1]

Lung Transplantation

Lung transplantation was initially used as treatment for pulmonary fibrosis and pulmonary hypertension, but the indications have evolved such that emphysema is the most common diagnosis leading to transplantation today. Lung transplantation for COPD and α_1-antitrypsin deficiency accounted for 60% of the almost 17,000 lung transplantations performed worldwide over the last decade.[29] The effect of lung transplantation on the survival of patients with COPD is not yet settled. Results from "The twenty-fourth official adult lung and heart-lung transplantation report-2007 from the Registry of the International Society for Heart and Lung Transplantation" found a post-transplantation survival for patients with COPD of 81.5% at 1 year, 64.0% at 3 years, and 49.0% at 5 years.[29] In fact for younger patients receiving bilateral lung transplantation, the survival is 94.9, 84.7, and 68.2% in those less than 50 years of age, and 93.0, 79.7, and 60.5% for those between ages 50 and 60 years at 1, 2, and 3 years, respectively.[30] In May 2005 a lung allocation system was created in the United

States, with aims to prioritize patients who are most likely to die on the waiting list. The goal are to optimizing overall survival benefit rather than the prior, less discriminating, listing system based on waiting time.[127] Efforts like this and other efforts have been implemented to help select patients who will benefit the most from transplant. Lung transplant improves survival in appropriately selected patients. Lung transplantation also improves exercise tolerance and quality of life in patients with severe COPD. [31]

Appropriate patients for lung transplant include patients whose predicted disease-related survival based on the Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE) index is worse than the predicted survival after transplantation. [32] Patients with a BODE index score of 7–10 have a median survival of about 3 years and should be evaluated for transplantation. Patients who are not candidates for endoscopic or surgical lung volume reduction, but have COPD with progressive disease, BODE index of 5 to 6, Pco2 > 50 mmHg or 6.6 kPa and/or Pao2 < 60 mmHg or 8.0 kPa, and FEV1 < 25% predicted should be referred for lung transplantation.[3] Additionally, patients who are hospitalized with COPD exacerbation complicated by hypercapnia (PaCO2 >50 mm Hg), who have a 2-year survival of only 49% should also be evaluated for lung transplantation.[33] Patients who have emphysema with FEV1 < 20% predicted and either homogeneous disease on high-resolution computed tomography scan (HRCT) or diffusion capacity (DlCO) < 20% predicted have a median survival of about 3 years with medical therapy and are at high risk of death after LVRS with little chance of functional benefit patients should be considered for transplantation.[10,34]

Recommended criteria for listing include one of the following: [3]

- BODE index > 7
- FEV1 < 15-20% predicted
- Three or more severe exacerbations during the preceding year
- One severe exacerbation with acute hypercapnic respiratory failure
- Moderate to severe pulmonary hypertension

Also patients who have multiple co morbidities or patients with pulmonary hypertension, hypoxemia, hypercapnia, and multiple disease exacerbations have reduced survival rates,[131,132] and so should be considered for lung transplantation. Lung transplantation consists of a morbid surgical procedure followed by life-long

immunosuppressive therapy. Candidates for lung transplantation should have the support system to be able to go through the process. (Table 4)

Table 3: Selection of candidates for lung transplantation

Who should be evaluated for lung transplantation?
• Patients with severe COPD who remain symptomatic despite optimal medical therapy
• Candidates whose predicted disease-related survival is less than the predicted survival after transplantation (81.5, 64.0, and 49.0% at 1, 3, and 5 year, respectively).[29]
• Patients who are hospitalized with a COPD exacerbation complicated by hypercapnia (PaCO2 ⩾ 50 mm Hg), who have a 2-year survival of only 49%.[32]
• Patients with a BODE index score of 7–10 (have a median survival of about 3 years)
• Patients with a median survival of about 3 years with medical therapy, high risk of death after LVRS with little chance of functional benefit.[10]
• Patients with additional risk factors for reduced survival (pulmonary hypertension, hypoxemia, and hypercapnia, and multiple disease exacerbations) [35]
• α1-antitrypsin deficiency
When to consider lung transplantation over LVRS
• FEV1 ≤20% predicted and either homogeneous disease or DlCO ≤20% predicted
• Lack of emphysema on HRCT
• TLC < 100% predicted
• RV < 150% predicted
• PaCO2 > 55 - 60 mm Hg
• PaO2 < 45 mm Hg
• 6MWD≤140 m, < 3 min unloaded pedaling on cycle ergometer
• Pulmonary hypertension
• Clinically significant bronchiectasis and/or recurrent pulmonary infections

6MWD: distance walked in 6 minutes; DLCO: diffusion capacity of carbon monoxide; HRCT: high-resolution computed tomography; LVRS: lung volume reduction surgery; RV: residual volume; TLC: total lung capacity.

Pulmonary function and gas exchange drastically improve after lung transplant. Hypoxemia and hypercapnia improve significantly and return to normal or near-normal values and almost all patients remain free of supplemental oxygen.[36-38] FEV1 increases from 15–20% predicted to 80–90% predicted in bilateral lung transplantation and to 50–60% predicted in ingle lung transplantation.[(133,134,135,136)] Exercise capacity increases after transplantation. The six-minute-walk distance doubles by 3–6 months after surgery, going from about 700–900 feet to about 1,300–1,700 feet. [37-39]

Trans diaphragmatic pressures improve with maximal sniff after lung transplantation, compared with similar patients with COPD not undergoing transplantation.[40]

There are sustained improvements in multiple dimensions of quality of life after lung transplantation including physical functioning, role function, social function, mental health, and health perceptions. Up to 90% of patients were satisfied by their decision to undergo transplantation.[41]

Lung transplantation results in greater short-term mortality and morbidity, a longer postoperative course and a predicted lower long-term survival as compared with patients undergoing LVRS, with a hazard ratio of 1.7. [140] This could be partly due to the fact that patients who undergo lung transplantation usually have more severe airflow obstruction with a mean FEV1 of 23.6 ± 8.5 vs. 31.9 ± 17%. Diaphragm dysfunction occurs in about 3.2–42.8% of patients after transplantation, possibly because of phrenic nerve dysfunction.[42]

Late post-transplantation complications such as bronchiolitis obliterans syndrome are frequent in patients who undergo lung transplant. The procedure is generally of longer duration, with a more frequent requirement for cardiopulmonary bypass.[39,43-45] Lung transplantation patients tend to have a longer hospital stay and more outpatient visits compared with patients undergoing LVRS.[46] Postoperative in-hospital stay after lung transplantation is 16–35 days as compared to just 10 days for LVRS.

Causes of early mortality after transplantation (within 30days).[29]

- Graft failure (28.3%)
- Non cytomegalovirus infections (20.3%)
- Cardiovascular complications (10.8%)
- Technical issues (8.2%)
- Acute rejection (4.7%

Table 4: Contraindications to lung transplantations

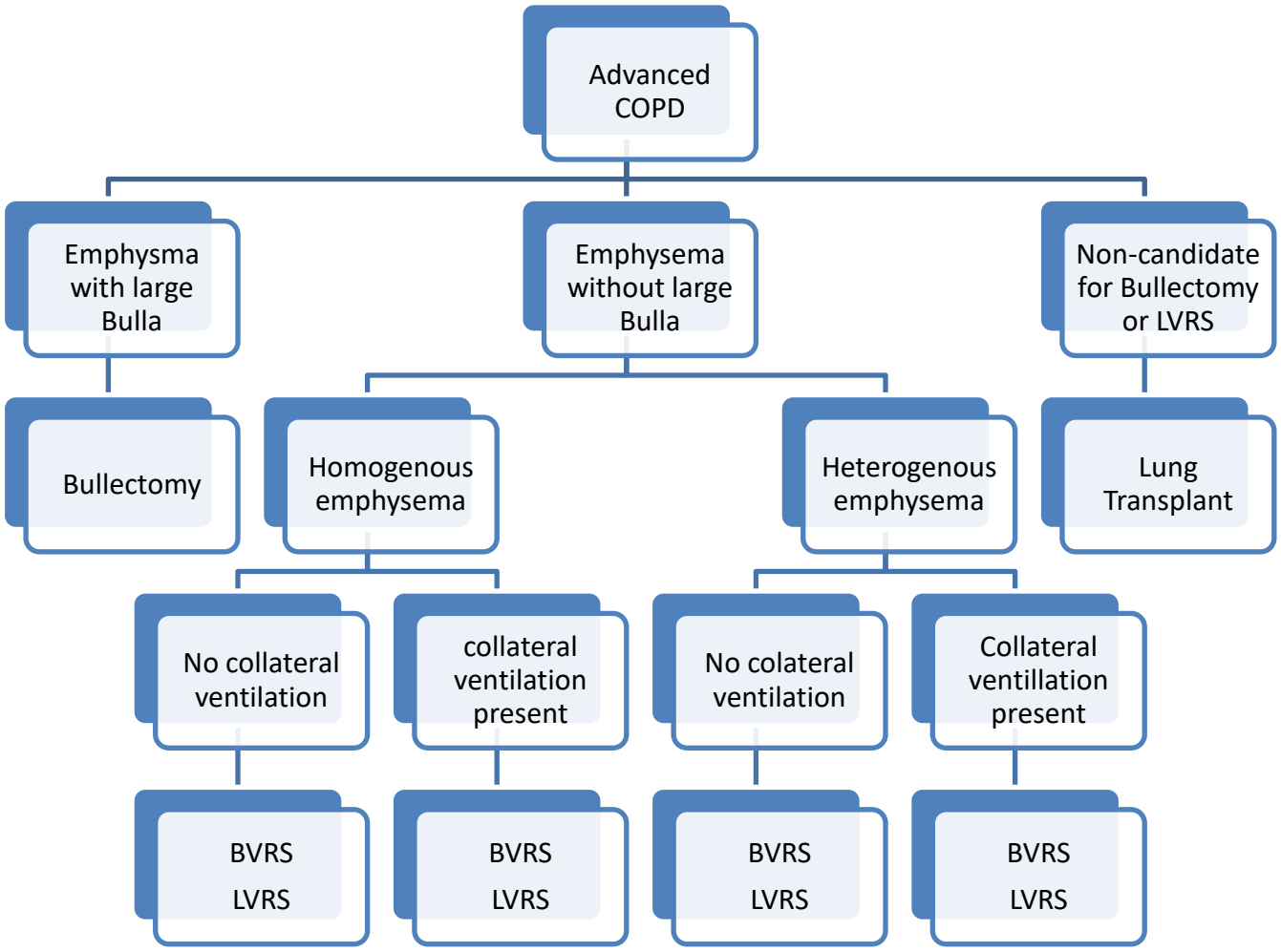
Absolute contraindications

- Comorbidities that precluding appropriate immunosuppressive therapy such as renal insufficiency, liver dysfunction, neuropathy, significant osteoporosis and uncontrolled diabetes
- Chronic active viral hepatitis B, hepatitis C with biopsy-proven histologic evidence of liver disease
- HIV infection
- Lack of social support
- Psychiatric conditions limiting long-term compliance
- Inability to maintain long-term follow-up
- Malignancy (with the exception of cutaneous squamous and basal cell tumors)
- Refractory gastroesophageal reflux disease
- Significant chest wall or spinal deformity
- Active substance use disorder or within the last 6 months

Relative contraindications

- Age older than 65 years
- Critical or unstable clinical condition (e.g., shock, mechanical ventilation or ECMO)
- Severely limited functional status with poor rehabilitation potential
- Colonization with highly resistant or highly virulent bacteria, fungi or mycobacteria
- Severe obesity defined as a BMI exceeding 30 kg/m^2
- Chronic mechanical ventilation
- Unstable extra pulmonary medical conditions that have not resulted in end-stage organ damage

Figure 1: Interventional, Bronchoscopic and Surgical Managements of Chronic Obstructive Pulmonary Disease[24]



Conclusions:

Surgical managements are not the first line management for patients with COPD, but the only potentially curative treatment for COPD is a surgical treatment. Within the past 5 years, several surgical techniques have been developed for the management of selective candidates with COPD. Pharmacological and non-pharmacological managements remain the initial treatments for COPD, but with the amount of progress noted in the surgical management, and the fact that surgical managements are the only curative treatments up to date for the treatment of COPD, there is a potential to change that trend in the future. There are strict criteria for the selection of patients who can undergo surgical management. These patients have to be carefully selected to make sure that the benefits from the selected surgical management will certainly outweigh the risks. Within the past five years, there has been major progress has been made on BVRS. This is an area in the surgical management of COPD with great potential.

Management of COPD requires a multidisciplinary team effort. Pulmonary and critical care specialists and internist most work pulmonary rehabilitation teams to optimize the care of patients with COPD. Once a patient meets the surgical criteria for the management of COPD, surgical consultation should be sorted right away for consideration. Major efforts are in progress to curb risk factors for COPD. Giving the rise in COPD despite all the efforts, more research and resources may still be needed to finally reduce the mortality and morbidity rates of COPD.

References

1. Meyers BF, Patterson GA. Chronic obstructive pulmonary disease. 10: Bullectomy, lung volume reduction surgery, and transplantation for patients with chronic obstructive pulmonary disease. *Thorax.* 2003;58(7):634-638.

2. AGUSTI A. Gold Reports 2020 - Global Initiative for Chronic Obstructive ... https://goldcopd.org › 2019/11 › GOLD-2020-REPORT-ver1.0wms.pdf. Published 2019/11.

3. Weill D. Lung transplantation: indications and contraindications. *J Thorac Dis.* 2018;10(7):4574-4587.

4. Clarenbach CF, Sievi NA, Brock M, Schneiter D, Weder W, Kohler M. Lung Volume Reduction Surgery and Improvement of Endothelial Function and Blood Pressure in Patients with Chronic Obstructive Pulmonary Disease. A Randomized Controlled Trial. *Am J Respir Crit Care Med.* 2015;192(3):307-314.

5. Lando Y, Boiselle PM, Shade D, et al. Effect of lung volume reduction surgery on diaphragm length in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1999;159(3):796-805.

6. Bellemare F, Cordeau MP, Couture J, Lafontaine E, Leblanc P, Passerini L. Effects of emphysema and lung volume reduction surgery on transdiaphragmatic pressure and diaphragm length. *Chest.* 2002;121(6):1898-1910.

7. Scott JP, Gillespie DJ, Peters SG, et al. Reduced work of breathing after single lung transplantation for emphysema. *J Heart Lung Transplant.* 1995;14(1 Pt 1):39-43.

8. Brath H, Lahrmann H, Wanke T, et al. The effect of lung transplantation on the neural drive to the diaphragm in patients with severe COPD. *Eur Respir J.* 1997;10(2):424-429.

9. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *Am J Respir Crit Care Med.* 1997;155(6):1984-1990.

10. Teschler H, Stamatis G. [NETT confirms clear survival advantages by lung volume reduction in predominantly apical emphysema with reduced ability to cope with stress]. *Pneumologie.* 2003;57(7):361-362.

11. Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. *Ann Thorac Surg.* 2006;82(2):431-443.

12. Krachman SL, Chatila W, Martin UJ, et al. Effects of lung volume reduction surgery on sleep quality and nocturnal gas exchange in patients with severe emphysema. *Chest.* 2005;128(5):3221-3228.

13. Kozora E, Emery CF, Ellison MC, Wamboldt FS, Diaz PT, Make B. Improved neurobehavioral functioning in emphysema patients following lung volume reduction surgery compared with medical therapy. *Chest.* 2005;128(4):2653-2663.

14. 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(21):2059-2073.

15. Fessler HE, Scharf SM, Ingenito EP, McKenna RJ, Jr., Sharafkhaneh A. Physiologic basis for improved pulmonary function after lung volume reduction. *Proc Am Thorac Soc.* 2008;5(4):416-420.

16. Ingenito EP, Loring SH, Moy ML, Mentzer SJ, Swanson SJ, Reilly JJ. Interpreting improvement in expiratory flows after lung volume reduction surgery in terms of flow limitation theory. *Am J Respir Crit Care Med.* 2001;163(5):1074-1080.

17. Keller CA, Ruppel G, Hibbett A, Osterloh J, Naunheim KS. Thoracoscopic lung volume reduction surgery reduces dyspnea and improves exercise capacity in patients with emphysema. *Am J Respir Crit Care Med.* 1997;156(1):60-67.

18. Sciurba FC. Early and long-term functional outcomes following lung volume reduction surgery. *Clin Chest Med.* 1997;18(2):259-276.

19. Gorman RB, McKenzie DK, Butler JE, Tolman JF, Gandevia SC. Diaphragm length and neural drive after lung volume reduction surgery. *Am J Respir Crit Care Med.* 2005;172(10):1259-1266.

20. Bloch KE, Li Y, Zhang J, et al. Effect of surgical lung volume reduction on breathing patterns in severe pulmonary emphysema. *Am J Respir Crit Care Med.* 1997;156(2 Pt 1):553-560.

21. Jorgensen K, Houltz E, Westfelt U, Ricksten SE. Left ventricular performance and dimensions in patients with severe emphysema. *Anesth Analg.* 2007;104(4):887-892.

22. Zuwallack R. The nonpharmacologic treatment of chronic obstructive pulmonary disease: advances in our understanding of pulmonary rehabilitation. *Proc Am Thorac Soc*. 2007;4(7):549-553.

23. Celli BR, Decramer M, Wedzicha JA, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. *Eur Respir Rev.* 2015;24(136):159-172.

24. Singh D, Agusti A, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. *Eur Respir J.* 2019;53(5).

25. Palla A, Desideri M, Rossi G, et al. Elective surgery for giant bullous emphysema: a 5-year clinical and functional follow-up. *Chest.* 2005;128(4):2043-2050.

26. Neviere R, Catto M, Bautin N, et al. Longitudinal changes in hyperinflation parameters and exercise capacity after giant bullous emphysema surgery. *J Thorac Cardiovasc Surg.* 2006;132(5):1203-1207.

27. Greenberg JA, Singhal S, Kaiser LR. Giant bullous lung disease: evaluation, selection, techniques, and outcomes. *Chest Surg Clin N Am.* 2003;13(4):631-649.

28. Lederer DJ, Arcasoy SM. Update in surgical therapy for chronic obstructive pulmonary disease. *Clin Chest Med.* 2007;28(3):639-653, vii.

29. Trulock EP, Christie JD, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report-2007. *J Heart Lung Transplant.* 2007;26(8):782-795.

30. Meyer DM, Bennett LE, Novick RJ, Hosenpud JD. Single vs bilateral, sequential lung transplantation for end-stage emphysema: influence of recipient age on survival and secondary end-points. *J Heart Lung Transplant.* 2001;20(9):935-941.

31. Patel N, DeCamp M, Criner GJ. Lung transplantation and lung volume reduction surgery versus transplantation in chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2008;5(4):447-453.

32. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005-1012.

33. Connors AF, Jr., Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med.* 1996;154(4 Pt 1):959-967.

34. Ramsey SD, Shroyer AL, Sullivan SD, Wood DE. Updated evaluation of the cost-effectiveness of lung volume reduction surgery. *Chest.* 2007;131(3):823-832.

35. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. *Am J Respir Crit Care Med.* 2001;164(3):358-364.

36. Levine SM, Anzueto A, Peters JI, et al. Medium term functional results of single-lung transplantation for endstage obstructive lung disease. *Am J Respir Crit Care Med.* 1994;150(2):398-402.

37. Sundaresan RS, Shiraishi Y, Trulock EP, et al. Single or bilateral lung transplantation for emphysema? *J Thorac Cardiovasc Surg.* 1996;112(6):1485-1494; discussion 1494-1485.

38. T5C4VTGBavaria JE, Kotloff R, Palevsky H, et al. Bilateral versus single lung transplantation for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg.* 1997;113(3):520-527; discussion 528.

39. Cassivi SD, Meyers BF, Battafarano RJ, et al. Thirteen-year experience in lung transplantation for emphysema. *Ann Thorac Surg.* 2002;74(5):1663-1669; discussion 1669-1670.

40. Wanke T, Merkle M, Formanek D, et al. Effect of lung transplantation on diaphragmatic function in patients with chronic obstructive pulmonary disease. *Thorax.* 1994;49(5):459-464.

41. Lanuza DM, Lefaiver C, Mc Cabe M, Farcas GA, Garrity E, Jr. Prospective study of functional status and quality of life before and after lung transplantation. *Chest.* 2000;118(1):115-122.

42. Dorffner R, Eibenberger K, Youssefzadeh S, et al. Diaphragmatic dysfunction after heart or lung transplantation. *J Heart Lung Transplant.* 1997;16(5):566-569.

43. McKenna RJ, Jr., Benditt JO, DeCamp M, et al. Safety and efficacy of median sternotomy versus video-assisted thoracic surgery for lung volume reduction surgery. *J Thorac Cardiovasc Surg.* 2004;127(5):1350-1360.

44. Pochettino A, Kotloff RM, Rosengard BR, et al. Bilateral versus single lung transplantation for chronic obstructive pulmonary disease: intermediate-term results. *Ann Thorac Surg.* 2000;70(6):1813-1818; discussion 1818-1819.

45. Haverich A. Experience with lung transplantation. In: *Ann Thorac Surg.* Vol 67. Netherlands1999:305-312.

46. Weinstein MS, Martin UJ, Crookshank AD, et al. Mortality and functional performance in severe emphysema after lung volume reduction or transplant. *Copd.* 2007;4(1):15-22.

