

RESEARCH ARTICLE

Surgical Therapies of the COPD

Vasileios Spyropoulos¹, Agathi Spiropoulou², Georgia Spyropoulou³, Dimosthenis Lykouras⁴, Kiriakos Karkoulias⁵, Kostas Spiropoulos⁶

^{1,2}Medical Student University of Patras

³Student of Pharmacy University of Nicosia Cyprus

^{4,5}Medical School University of Patras

⁶Emeritus Professor of Medicine University of Patras

Received: 09 May 2023 Accepted: 17 May 2023 Published: 24 May 2023

Corresponding Author: Kostas Spiropoulos, Emeritus Professor of Medicine University of Patras, Greece.

Abstract

The chronic obstructive pulmonary disease (COPD) includes specific details with chronic bronchitis and emphysematous pneumonic pathology. There are also asthma characteristic lesions that produce “chronic asthmatic bronchitis”. The main reason for this case, is smoking. The pathoanatomical abnormalities in COPD lead to disturbances in the ventilation/perfusion (v/q) ratio, leading to respiratory failure and hypoxemia. Furthermore, as the lungs over expand, respiratory remodeling leads to hypoventilation and respiratory failure II and hypercapnia. The treatment consists of medicines that are inhaled or taken from the body. In severe COPD cases where conventional therapeutic interventions have failed, satisfactory results are often achieved using novel intervention techniques. These are a) Bronchoscopic Thurmol Vapor Ablation (BTBA), b) Lung Volume Reduction Surgery (LVRS), c) Targeted Lung Conservation (TLD), d) Stem Cell Therapy, e) Lung Transplantation.

1. Introduction

The chronic obstructive pulmonary disease (COPD) is a heterogeneous group of diseases, which share the common feature of persistent airflow reduction. It is caused by the action of various causes, the most important being smoking, which damages the lungs through many but also well-defined mechanisms.

At this point it should be mentioned that the role of free radicals produced by smoking is very important. The COPD is characterized by narrowing of the airways (bronchus, bronchioles) due to bronchitis and damage to the lung parenchyma by emphysema. The coexistence of chronic bronchitis and emphysema lesions is the disease classification unit of COPD. These lesions disrupt the V/Q ventilation/perfusion relationship, leading to hypoxemia and lung dilatation, and in advanced stages hypercapnia and respiratory acidosis. The classic classification of COPD is Mild, Moderate and Severe - it is done

based on the value of FEV-1, the volume of air exhaled in the first second of a deep and vigorous exhalation. COPD is mild if FEV-1 is 60-79% of expected. If it is 40-59% of the expected COPD, it is classified as moderate, and if the FEV-1 is less than 40% of the expected COPD, it is classified as severe. Of course, there are other, more complex situations. However, what is described is satisfactory. Treatment is adjusted according to the severity of COPD. When mechanisms of “bronchial asthma” co-exist in COPD, this fact must be considered both in relation to disease severity and treatment. What does COPD treatment involve?

1. Stop smoking. This is the most interesting intervention
2. Inhaled medications and tablets to support respiratory function
3. Pulmonary resuscitation, improving respiratory function and respiratory muscles

Citation: Kostas Spiropoulos, Surgical Therapies of the COPD Archives of Pulmonology and Respiratory Medicine. 2023;6(1):01-09.

©The Author(s) 2023. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

4. Appropriate diet
5. Surgical treatment

2. Smoking Cessation

It is the most important factor to prevent the occurrence and development of diseases. If interruption occurs early, the disease course is interrupted before airway inflammation develops (1). If disruption occurs later, the outcome is less favorable than if inflammation persists (2, 3). However, it must be emphasized that smoking cessation at any age reduces mortality from the disease (4). Guidance on smoking cessation (5) includes consultation with a pulmonologist and medication support at a 'smoking cessation clinic'. Pharmacological support includes nicotine patches or "nicotine gum". Administration of bupropion, nortriptyline and clonidine (5) was also the last intervention. Likewise, in addition to smoking, other attractive factors should be avoided, such as: B. Exposure to toxic dusts, particles and gases that are characteristic of environmental or occupational pollution (6). Influenza and pneumococcal vaccinations reduce mortality (7,8)

3. Inhalation or other Drugs

Many COPD patients experience improvements in dyspnea and fatigue tolerance with bronchodilators (9). Bronchodilators are long-acting and double-acting drugs. The same applies to anticholinergic drugs, which are also short- or long-acting (10, 11, 12, 13, 14). Bronchodilators are administered through a special device (inhaler) (15). These drugs are received every 6 hours, or every 12 hours, or every 24 hours, whichever comes later.

3.1 Methyloxanthines

Theophylline is the only one used in COPD. It has a moderate bronchodilation effect (16). However, it has anti-inflammatory effects as well as cardiotoxic and diuretic effects (17, 18). We often use bronchodilators in combination (β_2 -agonists + anticholinergics) (19).

3.2 Corticosteroids

Administered in inhaled or tablet form or by intravenous infusion. Corticosteroid use appears to help in 10-15% of patients with COPD (20-23). Some formulations contain an inhaled bronchodilator and an inhaled corticosteroid in inhaled form (24).

3.3 Mucolytics

The COPD causes hypersecretion of bronchial secretions, exceeding 100 mL/day. In these cases, irritating substances (cigarettes or other

toxic substances) should not be inhaled. Acetylcysteine is commonly used as an expectorant in Europe (25). But it also has antioxidant properties. Expectorants: Administration of β_2 agonists and theophylline improves mucociliary clearance and aids expectoration (26).

3.4 Mucus Production Inhibitors

Growth factor receptor inhibitors seem to decrease mucus production. Drainage physiotherapy: If the secretion exceeds 30ml/day, it should be drained at an appropriate drainage point. Inhaled β_2 -stimulants should be given before (20-30 minutes) intervention by the physiotherapist (27, 28, 29).

3.5 Continuous Oxygen Therapy

Continuous oxygen therapy must be administered to patients in whom hypoxemia is observed due to V/Q disturbances. The daily duration is 12 or 17 hours/day. In severe cases, 24-hour administration is preferred. If hypoxemia occurs only during sleep, give O₂ during sleep. For hypoxemia during exhaustion, administer O₂ during daily activities using portable O₂ concentrators (30, 31, 32, 33).

4. Pulmonary Resuscitation

Trying to get the best out of the patient. That's why it's considered an important help for patients with severe COPD. Benefits to patients are improved quality of life, shorter hospital stays, and improved physical function (34). However, FEV-1 usually does not improve. Interestingly, despite no improvement in airflow, resuscitation had a much greater health impact than medical therapy (35).

The patient trains the muscles in general, but also trains the respiratory muscles in particular. As with all training programs, results are lost at the end of the program. Continuing with the program is the main reason for maintaining results.

Patients whose arterial O₂ partial pressure drops during exercise should be given O₂. Hb saturation below 88% during exercise indicates oxygen therapy (36). Administration of bronchodilators appears to improve exercise capacity.

Loosing weight also seems to help (37). At home, it makes sense to train the respiratory muscles using equipment that increases the required inspiratory and expiratory pressures at exercise. Ideally, the duration should be 30 minutes/day.

This improves respiratory muscle function and reduces long-distance shortness of breath in asthma (38, 39).

Importantly, 50% of patients do not complete the rehabilitation program. Even among those patients who completed the program, the results disappeared within a few months of stopping exercise. It is fun to practice having the patient open their lips and exhale. Gains include reduced respiratory rate, increased tidal volume (Tv), and reduced alveolar air trapping. On exhalation (40, 41, 42). PO₂ is also sometimes elevated (43). Practicing diaphragmatic breathing appears to help (44).

4.1 Appropriate Diet

Some patients with severe COPD with predominantly emphysematous lesions lost significant weight, and some exhibited cachexia (45). These patients exhibit decreased muscle mass.

These patients exhibit decreased muscle mass. The reasons for this are manifold (46, 47). 15-20% increased energy requirement while stationary (48, 49). The main effect of weight loss is to weaken the inspiratory and expiratory muscles (50).

This fact affects the prognosis of the disease and its behavior. Improved nutrition can improve the condition of the respiratory muscles, as well as other muscles. This improvement is manifested in weight gain (51, 52).

Unfortunately, gaining weight is difficult and requires serious effort. Use of anabolic androgens improves muscle strength and increases body weight (53, 54). In contrast, there are insufficient data to support the routine administration of these agents.

4.2 Antibiotics

Less than 50% of the COPD are caused by bacterial infection with pyogenic organisms that normally colonize the bronchial tree. bacteria as *Streptococcus pneumoniae* and *Moraxella catarrhalis* (56). During an attack, the number of microorganisms in patients' bronchial secretions is higher compared to the number of microorganisms during the interval between attacks (57).

Cultures of bronchial secretions provide information on the type of microorganisms, but not on the number of these microorganisms (58). If the patient develops shortness of breath, cough, and purulent sputum, this is an indication for antibiotics (59, 60).

Typically, 7–10 days of trimethoprim/sulfamethoxazol, ampicillin, and tetracycline are effective. If this empiric treatment fails, bronchoscopy is performed, during which, under abstinent conditions, bronchial secretions are collected,

cultures and antibiotic profiles are performed to isolate responsible microorganisms and determine their precise susceptibility to antibiotics.

5. Recent Treatment of COPD

In some cases, especially in severe COPD, conventional treatment does not lead to satisfactory results and does not ensure a satisfactory quality of life for the patient. In these cases, invasive treatments are available such as:

1) Bronchoscopic Thermal Vapor Ablation (BTVA), which involves blocking the bronchi with “boiled” sterile water. Using this method, endoscopic lung volume reduction (ELVR), or lung volume reduction, is performed. Endoscopic steam delivery induces an inflammatory response in the irregular bronchi leading to their obstruction. This reduces the volume of the lung, as the proper lung parenchyma is selected, while the healthy lung is overstretched. This method is suitable for patients with emphysema mainly located in the upper lobe, or FEV-1 between 20-45%, and residual volume (RV) > 20% expected value. Preoperatively, it is necessary to accurately determine that the bronchi of the corresponding lung segment must be closed. The surgery is performed under general anesthesia or hypnosis. After surgery, the patient must be monitored because the inflammatory response induced by the superheated steam initially aggravates the patient's symptoms and general condition (61, 62, 63, 64, 65, 66, 67, 68, 69, 70). The equipment needed are: a bronchoscope, a steam generator, and a balloon-terminated catheter with which we close the segmental bronchi that deliver the steam. Balloons should be inflated for at least 8 minutes. This process can then be repeated for the next segment of the cycle.

These patients were treated with corticosteroids and broad-spectrum antibiotics over 14 days to avoid bacterial infections that could complicate the patient's condition. Possible complications are: a) exacerbation of COPD, b) pneumonia, (66), c) hemoptysis (63, 66), d) bronchopneumonia, and e) pneumothorax (66).

6. Surgery to Reduce Lung Volume Lung Volume Reduction Surgery (Lvrs)

This is achieved through surgical techniques that remove large amounts of emphysematous tissue. It appears that this surgical technique helps improve respiratory capacity, vital capacity, and overall quality of life in selected patients (71, 72).

The procedure reduces the size of an overextended emphysematous lung, thus enlarging the remaining healthy lung parenchyma. The LVRS surgical technique is used in patients with severe emphysema, severe dyspnea, and signs of severe air trapping in the alveoli (73). The effectiveness of surgery depends on the location and extent of the emphysematous lesion, as well as on the patient's ability to recover. And his ability to cope with the inconvenience of surgery. According to the National Emphysema Treatment Trial (NETT), 4 patient groups with different risks and benefits of LVRS have been defined.

Group 1: Predominantly upper lobe emphysema, barely beyond surgery.

Group 2: Also, this group showed upper lobe emphysematous lesions but had a high fatigue capacity. This group appeared to respond better to surgery than to drugs.

Group 3: Somatic injury and low recovery characterized by diffuse emphysema. This group had similar expected survival rates regardless of whether they were undergoing surgery or taking medications.

Group 4: Characterized by diffuse lesions and high exercise capacity. This group had a shorter survival time after surgery compared with medical treatment (73).

In LVRS surgery, 30% of the lung parenchyma is resected from each lung. This makes the lungs smaller and work better. The ventilation/perfusion V/Q ratio is also improved. LVRS is performed after sternotomy or thoracoscopically.

In sternotomy, tissue from both lungs is removed simultaneously during thoracoscopic examination, and 3-5 holes are made in the intercostal space and in both ribcages. A thoracoscope was inserted and diffuse lesions were removed from both lungs (73).

Before surgery, patients should undergo a detailed examination including: chest radiograph, spirometry, plethysmography, diffusion capacity measurement (DLCO), blood gas measurements (PaO₂ and PaCO₂), electrocardiogram (ECG), six minutes walking test (6MWT), and cardiorespiratory fatigue.

The risks of surgery are pneumothorax, pneumonia, heart attack, bleeding and death. Lung volume reduction (LVR) is also carried out through bronchoscopy, and a special valve is placed in the pre-selected bronchi to block, so that the emphysema area can be satisfactorily expanded, and the healthy area can be expanded.

This improves ventilation perfusion, V/Q ratio, and arterial blood gases (74, 75, 76). Therefore, electrodes are used to disrupt the branches of the vagus nerve. The vagus nerve is known to cause contraction of the respiratory muscles and narrowing of the airways, but also increases mucus secretion, which exacerbates narrowing and obstruction of the airways. In COPD patients, the vagus nerve is often overactive, leading to bronchospasm and excess mucus production, causing symptoms such as coughing, shortness of breath, wheezing, and lung heaviness.

By using the methods described above, patients' symptoms and quality of life appear to improve. The beneficial effects are also believed to reduce the need for long-term use of anticholinergic drugs, and the procedure is simple and painless for the patient, taking about an hour.

The bronchoscope is inserted into the bronchi corresponding to the branch of the vagus nerve that we want to destroy. After the bronchoscope is in the correct position, an electrode is inserted through which a current is passed, causing heating to disrupt the adjacent space, which must be 10-12 mm away from the electrode.

7. Stem Cell Therapy (SCT)

Stem cells have the unique ability to develop into any cell in the body through the process of differentiation. They are given intravenously and "find" damaged tissue in various organs. When given to patients with COPD, the stem cells can repair damaged lungs. In addition, stem cells display anti-inflammatory properties, thus "cleaning" the airways and suppressing inflammation.

According to a study by the American Lung Institute. It appears that 82% of treated patients experienced significant improvements in quality of life, breathing capacity, and walking ability (73). It appears that this approach works better with patients who need ventilators or lung transplants.

The treatment appeared to be safe, with no toxic effects or deaths occurring. Stem cell administration, even without HLA compatibility, appears to be effective. Treatment costs \$25,000 and is not covered by insurance (78, 79, 80).

8. Lung Transplantation

For some people with severe COPD, lung transplantation may help when drugs and other treatments have not worked. Surgery has risks, such

as graft rejection and long recovery times from surgery (81). The University of California and the University of San Francisco propose the following criteria for selecting patients for lung transplantation.

- i. The age of bilateral transplantation is under 60 years old, and the age of unilateral transplantation is under 65 years old
- ii. The estimated survival time is at least 18-24 months.
- iii. No other serious diseases.
- iv. History upon specific drug tolerance.
- v. Emotional stabilization and perception of quality of life after lung transplantation (82). The risks of transplantation are: 1) Bleeding 2) Airway obstruction 3) infection 4) pulmonary vein obstruction 5) Pulmonary edema
- vi. Pulmonary embolism
- vii. Transplant rejection (83)

After the transplantation, immunosuppressive drugs are given. The patient was transferred to the ER, several hours a day. Pain medication is also given. After leaving the ER, perform pulmonary resuscitation procedures. Attempt to mobilize immediately to prevent pulmonary embolism. After discharge, frequent visits to the post-transplant clinic were followed by a 2-day hospital stay for complete respiratory control (54). If all goes well, survival can range from 5 to 6 years (84).

9. Conclusion

1. COPD is a multifactorial disease
2. Drugs adapted to the severity of the disease usually yield satisfactory results.
3. When drugs are ineffective, invasive treatment can be used for special populations, mainly critically ill patients.
4. Smoking cessation is the mainstay of treatment.

10. References

1. Anthonisen NR, Connett JE, Kiley JP, et al : Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1 . JAMA 272: 1497 – 1505, 1994.
2. Turato G, Di Stefano A, Maestrelli P, et al : Effects of smoking cessation on airway inflammation chronic bronchitis. A J Respir Crit Care Med 152: 1262 – 1267, 1995.
3. Rutgers SR, Postma DS, ten Hacken NH, et al: Ongoing airway inflammation in patients with COPD who do not currently smoke. Thorax 55 : 12–18, 2000.
4. Department of Health and Human Services : Health Benefits of Smoking Cessation : A Report of the surgeon General. Publication (CDC) 90 – 8416. Washington, DC : Department of Health and Human Services, 1990.
5. Flore MC : U.S. Public Health Service clinical practice guideline : Treating tobacco use and dependence. Respir Care 45 : 1200 – 1262, 2000.
6. Dominici F, McDermott A, Zeger SL, Samet JM: Airborne particulate matter and mortality: Timescale effects in four U.S. cities. A J Epidemiol 157 : 1055–1065, 2003.
7. Nichol KL, Argolis KL, Wuorenma J, Von Sternberg T : The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 331 : 778 – 784, 1994.
8. MMWR : Prevention and control of influenza : Recommendation of the Advisory Committee on Immunization Practices (ACIP); Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 47 (RR – 6) : 1 – 26, 1998.
9. O’ Donnell DE : Assessment of bronchodilator efficacy in symptomatic COPD : Is spirometry useful ? Chest 117 : 42S – 47S, 2000.
10. Johnson M, Rennard S : Alternative mechanisms for log – acting beta (2) – adrenergic agonists in COPD. Chest 120 : 258 – 270, 2001.
11. Santa Cruz R, Landa J, Hirsch J, et al : Tracheal mucous velocity in normal man and patients with obstructive lung disease : Effects of terbutaline. Am Rev Respir Dis 109 : 458 - 463, 1974.
12. Nava S, Crotti P, Gurrieri G, et all : Effect of a β_2 – agonist (Broxaterol) on respiratory muscle strength and endurance in patients with COPD irreversible airway obstruction. Chest 101 : 113– 140, 1992.
13. Calverley P, Pauwels R, Vestbo J, et al : Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease : A randomized controlled trial. Lancet 361 : 449 – 456, 2003.
14. Xiao RP : Beta – adrenergic signaling in the heart: Dual coupling of the beta2 – adrenergic receptor to G (s) and G (i) proteins. Sci STKE 2001: RE15, 2001.
15. Au DH, Curtis JR, Every NR, et al : Association between inhaled beta – agonists and the risk of unstable angina and myocardial infarction. Chest 121 : 846 – 851, 2002.

16. Barnes PJ: Theophylline: New perspectives for an old drug. *Am J Respir Crit Care Med* 167: 813–818, 2003.
17. ZuWallach RL, Mahler DA, Reilly D, et al: Salmeterol plus theophylline combination therapy in the treatment of COPD. *Chest* 119:166–1670, 2001.
18. Rossi A, Kristufek P, Levine BE, et al : Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow – release theophylline in the treatment of COPD. *Chest* 121:1055–1069, 2002.
19. Bellia V, Foresi A, Bianco S, et al :: Efficacy and safety of oxitropium bromide, theophylline and their combination in COPD patients. A double – blind, randomized, multicenter study (BREATH Trial). *Respir Med* 96 : 881 – 889, 2002.
20. Vestbo J, Sorensen T, Lange P, et al: Long–term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: A randomized controlled trial. *Lancet* 353:18119– 1823, 1999.
21. Burge PS, Calverley PM, Jones PW, et al: Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: The ISOLDE trial. *BMJ* 320: 1297 – 1303, 2000.
22. Pauwels RA, Lofdahl CG, Laitinen LA, et al: Long–term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 340 : 1948 – 1953, 1999.
23. The Lung Health Study Research Group : Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 343: 1902 – 1909, 2000.
24. Szafranski W, Cukier A, Ramirez A, et al : Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 21 : 74 – 81, 2003.
25. Babolini G, Blasi A, Cornia G, et al : Long – term oral acetylcysteine in chronic bronchitis, a double – blind controlled study. *Eur J Respir Dis* 111 : 93 – 108, 1980.
26. Hirsch SR, Viernes PF, Kory EC : The expectorant effect of glyceryl guaiacolate in patients with chronic bronchitis. *Chest* 63 : 9 – 14, 1973.
27. Marini JJ, Tyler ML, Hudson LD, et al : Influence of head – dependent positions on lung volumes and oxygen saturation in chronic airflow obstruction. *Am Rev Respir Dis* 129 : 101 – 105, 1984.
28. Sutton PP, Gemmell HG, Innes N, et al : Use of nebulized saline and nebulized terbutaline as an adjunct to chest physiotherapy. *Thorax* 43:57–60, 1988.
29. Faling LJ, Snider GL : Treatment of chronic obstructive pulmonary disease. In Simmons D (ed): *Current Pulmonology*. Chicago. Year Book, 1989, pp 209 – 263.
30. Kvale PA, Cugeli DW, Anthonisen NR, et al:Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Ann Intern Med* 93: 391–398, 1980.
31. Hearon RK, Grant I, McSweeney J, et al: Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med* 143: 1941 – 1947, 1983.
32. Cotes JE, Gilson JC : Effect of oxygen on exercise ability in chronic respiratory insufficiency. *Lancet* I: 872 – 876, 1956.
33. Woodcock AA, Gross ER, Gellert AA, et al : Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Engl J Med* 305: 1611 – 1616, 1981.
34. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel: Pulmonary rehabilitation; join ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, American College of Chest Physicians, American Association of Cardiovascular and Pulmonary Rehabilitation. *Chest* 112:1363–1396, 1997.
35. Finnerty JP, Keeping I, Bullough I, Jones J : The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. *Chest* 119 : 1705 – 1710, 2001.
36. American Thoracic Society: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 136 : 225 – 244, 1987.
37. Ries A, Ellis B, Hawkins R: Upper extremity exercise training in chronic obstructive pulmonary disease. *Chest* 93 : 688 – 692, 1988.
38. Celli B: Training and the respiratory muscles. In Marini JJ, Roussos C (eds) : *Ventilatory Failure Update in Intensive Care and Emergency Medicine*. Berlin : Springer – Verlag, 1991.
39. Lotters F, van Tol B, Kwakkel G, Gosselink R : Effects of controlled inspiratory muscle training in patients with COPD : A meta – analysis. *Eur Respir J* 20 : 570 – 576, 2002.
40. Weiner P, Magadle R, Beckerman M, et al : Maintenance of inspiratory muscle training in COPD patients: Once year follow–up. *Eur Respir J* 23:61–65, 2004.
41. Faling LJ: Pulmonary rehabilitations: Physical modalities. *Clin Chest Med* : 7: 599 – 618, 1986.

42. Ingram RH Jr, Schilder DP : Effect of pursed lips expiration on the pulmonary pressure – flow relationship in obstructive lung disease. *Am Rev Respir Dis* 96 : 381 – 388, 1967.
43. Tiep BL, Burns M, Kao D, et al : Pursed lips breathing training using ear oxymetry. *Chest* 90 : 218 – 221, 1986.
44. Sharp JT, Drutz WS, Moisan T, et al : Postural relief of dyspnea in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 122: 201 – 211, 1980.
45. Openbrief DR, Irwin MM, Rogers RM, et al : Nutritional status and lung function in patients with emphysema and chronic bronchitis. *Chest* 83: 17 – 22, 1983.
46. Donahoe M, Rogers RM, Wilson DO et al : Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 140 : 385 – 391, 1989.
47. Goldstein S : Nitrogen and energy relationships in malnourished patients with emphysema. *Am Rev Respir Dis* 138: 636 – 644, 1988.
48. De Godoy I, Donahoe M, Calhoun WJ, et al: Elevated TNF – alpha production by peripheral blood monocytes of weight – losing COPD patients. *Am J Respir Crit Care Med* 153 : 633 – 637, 1996.
49. Di Francia M, Barbier D, Mege JL, Orehek J : Tumor necrosis factor – alpha levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 150 : 1453 – 1455, 1994.
50. Rochester DF, Esau SA : Malnutrition and the respiratory system. *Chest* 85 : 411 – 415, 1984.
51. Wilson D: Nutritional intervention in malnourished patients with emphysema. *Am Rev Respir Dis* 134 : 672 – 677, 1986.
52. Whittaker JS, Ryan CF, Buckley PA, et al : The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. *Am Rev Respir Dis* 142: 283 – 288, 1990.
53. Creutzberg EC, Wouters EF, Mostert R, et al : A role for anabolic steroids in the rehabilitation of patients with COPD ? A double – blind, placebo – controlled, randomized trial. *Chest* 124 : 1733 – 1742, 2003.
54. Yeh SS, DeGuzman B, Kramer T : Reversal of COPD– associated weight loss using the anabolic agent oxandrolone. *Chest* 122 : 421 – 428, 2002.
55. Ambrosetti M, Ageno W, Spanevello A, et al: Prevalence and prevention of venous thromboembolism in patients with acute exacerbations of COPD. *Thromb Res* 112: 203 – 207, 2003.
56. Fagon JY, Chastre J, Trouillet JL, et al : Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. *Am Rev Respir Dis* 142: 1004 – 1008, 1990.
57. Chodosh S: Treatment of acute exacerbation of chronic bronchitis: State of the art. *Am J Med* 91 (Suppl): 87 – 92, 1991.
58. Murray PR, Washington JA : Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 50: 339 – 344, 1975.
59. Anthonisen NR, Manfreda J, Warren CPW, et al: Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease . *Ann Intern Med* 106: 196 – 204, 1987.
60. Sethi S : Infectious exacerbations of chronic bronchitis: Diagnosis and management. *J Antimicrob Chemother* 43 (Suppl A): 97 – 105, 1999.
61. Herth FJF, Slebos Dj, Criner GJ, Shah PL : Endoscopic lung volume reduction an expert panel recommendation – update 2017. *Respiration* 2017; 94: 380 – 388.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

62. Snell GI, Hopkins P, Westall G, Holsworth L, Carle A, Williams TJ : A feasibility and safety study of bronchoscopic thermal vapor ablation: a novel emphysema therapy. *Ann Thorac Surg* 2009; 88: 1993 – 1998.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

63. Snell G, Herth FJ, Hopkins P, Baker KM, Witt C, Gotfried MH, Valipour A, Wagner M, Stanzel F, Egan JJ, Kesten S, Ernst A : Bronchoscopic thermal vapor ablation therapy in the management of heterogeneous emphysema. *Eur Respir J* 2012; 39 : 1326 – 1333.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

64. Gompelmann D, Eberhardt R, Ernst A, Hopkins P, Egan J, Stanzel F, Vallpour A, Wagner M, Witt C, Baker KM, Gotfried MH, Kesten S, Snell G, Herth FJ : the localized inflammatory response to bronchoscopic thermal vapor ablation. *Respiration* 2013; 86: 324 – 331.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

65. Vallpoyr A, Herth FJ, Eberhardt R, Shah PL, Gupta A, Barry R, Henne E, Bandyopadhyay S, Snell G: Design of the randomized, controlled sequential staged treatment of emphysema with upper lobe predominance (STEP – UP) study. *BMC Pulm Med* 2014; 14: 130.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

66. Herth FJ, Valipour A, Shah PL, Eberhardt R, Grah C, Egan J, Ficker JH, Wagner M, Witt C, Liebers U, Hopkins P, Gesierich W, Phillips M, Stanzel F, McNulty WH, Petermann C, Snell G, Gompelmann D : Segmental volume reduction using thermal vapour ablation in patients with severe emphysema : 6 – month results of the multicenter, parallel – group, open – label, randomized controlled STEP – UP trial. *Lancet Respir Med* 2016; 4: 185 – 193.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

67. Shah PL, Gompelmann D, Valipour A, McNulty WH, Eberhardt R, Grah C, Egan J, Ficker JH, Wagner M, Witt C, Liebers U, Hopkins P, Gesierich W, Phillips M, Stanzel F, Petermann C, Strange C, Snell G, Herth FJ: Thermal vapour ablation to reduce segmental volume in patients with sever emphysema: STEP – UP 12 Month results. *Lancet Respir Med* 2016; 4: e44 – e45.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

68. Gompelmann D, Hesussel CP, Eberhardt R, Snell G, Hopkins P, Baker K, Witt C, Valipour A, Wagner M, , Stanzel F, Egan J, Ernst A, Kesten S, Herth FJ: Efficacy of bronchoscopic thermal vapor ablation and lobar fissure completeness in patinents with heterogeneous emphysema. *Respiration* 2012; 83: 400 – 406.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

69. Gompelmann D, Eberhardt R, Schuhmann M, Valipour A, Shah PL, Herth FJ, Kontogianni K :

Lung volume reduction with vapor ablation in the presence of incomplete fissures : 12 – month results from the STEP – UP randomized controlled study. *Respiration* 2016; 92 : 397 – 403.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

70. Gompelmann D, Eberhardt R, Herth FJ : Technology update : bronchoscopic thermal vapor ablation for managing severe emphysema. *Med Devices (Auckl)* 2014; 7: 335 – 341.

External Resources

> Pubmed/Medline (NLM)

>Crossref (DOI)

71. Perikleous P • Sharkey • Oey I. • et al. Long – term survival and symptomatic relief in lower lobe lung volume reduction surgery. *Respir J Cardiothprac Surg.* 2017; 52 : 982 – 988.

72. Fishman A. • Martinez F. • Naunheim K. • et al. • National Emphysema Treatment Trial Research Group *N Engl J Med.* 2003; 348: 2059 – 2079 View in Article Scopus 1651 • PubMed • Crossref • Google Scholar

73. Bendixen M • Jorgensen O.D. • Kronborg C. • Andersen C. • Licht P.B. Postoperative pain and quality of life after lobectomy vua video – assisted thoracoscopic surgery of anterolateral thoracotomy for early – stage lung cancer : randomized controlled trial. *Lancet Oncol.* 2016; 17: 836 – 844

View in Article Scopus (511) • PubMed • Abstract • Full Text PDF • Google Scholar

74. Criner G.J. • Sue R. • Wright S. • et al. A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). *A J Respir Crit Care Med.* 2018; 198: 1151 – 1164

View in Article Scopus (158) • PubMed • Crossref • Google Scholar

75. Eichhorn M.E. • Gompelman D. • Hoffman H. • et al. Consolidating lung volume reduction surgery after endoscopic lung volume reduction failure. *Ann Thorac Surg.* 2021; 111: 1858 – 1865

View in Article Scopus (4) • PubMed • Abstract • Full Text PDF • Google Scholar

76. Reis F.P. • Costa A.N. • Lauricella L.L. • Terra R.M. • Pego – Fernandes P.M. Intraoperative support with venovenous extracorporeal membrane oxygenation for complex thoracic oncologic resection. *J Bras Pneumol.* 2020; 46e20180416

View in Article Scopus (3) • Crossref • Google Scholar

77. Coleman J, (n.d.). Autologous Stem Cell Therapy & its Effects on COPD : A Pilot Sudy. Lung Institute – White Paper. https://lunginstitute.com/wp-content/uploads/2016/01/160113_White Paper.pc
78. Global Initiative For Chronic Obstructive Lung Disease (GOLD). (2021). 2021 Report : Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Retrieved from : <https://goldcopd.org/wp-content/uploads/2021/21/GOLD-2021v1.7-FINAL-revised-2021Jan29.pdf>
79. National Heart, Lung and Blood Institute. (2018). COPD: Diagnosis and management. Retrieved from <https://nhlbi.nih.gov/health-topics/copd-diagnosis-and-management>
80. International Society for Stem Cell Research (2021). Stem cell therapies for COPD. Retrieved from: <https://www.isscr.org./patients/diseaseinformation/copd>
81. Trulock EP, Edwards LB, Taylor DO, et al: The Registry of the International Society for Heart and Lung Transplantation : Twenty – first official adult lung and heart – lung transplant report – 2004. *J Heart Lung Trasplant* 23 : 804 – 815, 2004.(<http://www.isHLT.org/registries/quarterlyDataReport.asp>). International Society for Heart and Lung Transplantation official website also holds thiw material.
82. Madill J, Gutierrez C, Crossman J, et al: Toronto Lung Transplant Program: Nutritional assessment of the lung transplant patient: body index as a predictor of 90 – day mortality following transplantation. *H Heart Lung Transplant* 20: 288 – 296, 2001.
83. Kanasky WF Jr, Anton SD, Rodriguez JR, et al: Impact of body weight on long – term survival after lung transplantation. *Chest* 121: 401 – 406, 2002.
84. Lillihei CW: In discussion of Wildevuur CRH, Benfield JRA: A review of 23 human lung transplantations by 20 surgeons. *Ann thorac Surg.* 9: 489 – 515, 1970.