Emphysema and Bronchodilators

**Abstract**

Emphysema is a severe manifestation of COPD. It affects the alveoli and parenchymal cells of the lungs, causing contraction of the smooth muscles. The main symptoms of emphysema include low oxygen saturation level, respiratory distress and high respiratory rate. The lungs' alveoli play an essential role in storing oxygen, followed by oxygen distribution to the corners of the body. In emphysema, the lungs' alveoli fail to conduct their vital functions, causing respiratory distress. The activation of the hypersensitivity reactions is the main reason underlying such alveolar dysfunction. Bronchodilators, a class of beta2 agonists, are frequently used as the first line of treatment for emphysema. It is administered by inhalation. It works by causing dilation or relaxation of the smooth muscle cells of the airways. The side effects of bronchodilators include arrhythmias, tremors, and hypokalaemia. Special consideration needs to be taken in case of cardiac complications like tachycardia. Thus, for the management of emphysema, the contradictions, side-effects and other lifestyle factors need to be considered to improve the outcome of care.

# Introduction

Emphysema is a type of Chronic Obstructive Pulmonary Disease (COPD). Emphysema is a pathological diagnosis affecting air spaces distal to the terminal bronchiole (Humphries et al., 2020). It is characterized by abnormal yet permanent enlargement of the lung spaces with the destruction of their in the absence of fibrosis (Humphries et al., 2020). The destruction of lung parenchyma in emphysema causes loss of elasticity of the lungs, reducing its oxygen-carrying capacity and manifesting as breathing problems (Humphries et al., 2020). The following essay will discuss emphysema and the pharmacological therapy that is found to be effective for treating this respiratory disease. The paper will begin with the normal physiology of the lungs, which will be linked further with the pathophysiology of the disease. The next part of the paper will highlight the pharmacological management of the disease. A bronchodilator is selected here as a pharmacological intervention. Overall this essay will provide an overview of emphysema and its management.

# Physiology of the Lungs

Emphysema is a respiratory problem targeting the lungs. Lungs are the foundational organs of the respiratory system that facilitates gaseous exchange from the external environment to the bloodstream (Powers & Dhamoon, 2019). The oxygen gets transported through the lungs' alveoli into the capillary network, entering the arterial system and making final perfusion inside the tissues (Powers & Dhamoon, 2019). Emphysema, a type of severe COPD, mainly affects the lungs' alveoli. Alveoli are balloon-shaped structures that look like clusters of grapes and are present at the end of the respiratory tract. Their role is to expand while inhalation and shrink during exhalation. The tiny alveoli sacs are the site of gaseous exchange (Powers & Dhamoon, 2019). Emphysema makes these small alveolar sacks into large openings and reduces the elasticity of the alveoli causing respiratory distress. Alveoli are polygonal in shape, and each alveolus shares a common wall with the neighbours (Basil et al., 2020). The wall shared by two neighbouring alveoli is known as the inter-alveolar spectrum, and it consists of two types of epithelial cells, namely type I and type II. Type 1 pneumocystis covers 95% of the lungs' alveoli, whereas type II covers less than 5% (Basil et al., 2020).

# Emphysema Pathophysiology

Emphysema causes damage to the distal airways to the terminal bronchiole, acinus that includes respiratory bronchiole, alveolar ducts, alveolar sacs and alveoli. The reason behind such damage is smoking (Amariei et al., 2019). The part of the acinus affected determines the sub-type of emphysema. Centrilobular damage of the proximal acinar is a common type of emphysema and is associated with smoking among workers in coal mines. Panacinar is the second most common emphysema due to alpha-one antitrypsin deficiency (Rodrigues et al., 2021). Distal acinar or paraseptal emphysema occurs alone or in association with panacinar and centrilobular emphysema. Distal acinar, when occurring alone, is associated with spontaneous pneumothorax among young adults (Rodrigues et al., 2021).

Hypersensitivity reaction followed by complement activation is responsible for the gradual damage of the lungs' alveoli in emphysema. Long-term exposure to smoke causes activation of macrophages, neutrophils and T-lymphocytes (Leap et al., 2021). At first, the macrophages are activated, causing the release of the neutrophil chemotactic factors, leukotriene B4 and interleukin-8. This is followed by neutrophil activation of multiple proteinases and subsequent mucus hyperactivation. Mucus hyperactivation causes the release of elastase (neutrophil-derived proteases) (Leap et al., 2021). Elastin is the standard extracellular matrix component that maintains lung integrity. Elastase destroys the integrity of the elastin by destroying the connective tissues of the lungs, causing enlargement of the airspaces, one of the crucial hallmarks of emphysema (Santus et al., 2019). Enlargement of the airspaces reduces the oxygen-carrying capacity of the lungs, leading to respiratory distress. Cytotoxic T-cells release TNF-alpha and perforins, destroying the epithelial cells of the alveolar walls, again decreasing the lung capacity (Santus et al., 2019).

# Bronchodilator

A bronchodilator is the first-line of drug that is used for the treatment of emphysema. It belongs to the class of beta2 agonists. **The bronchodilators are administered regularly by inhalation** to reduce the acute exacerbations of emphysema by increasing the vital capacity (Barjaktarevic et al., 2019). It works by causing dilation or relaxation of the smooth muscle cells of the airways; thus, **named broncho-dilators**. Relaxation of the smooth muscle cells of the lungs increases the oxygen-carrying capacity and exercise tolerance. Short-acting beta2 agonists (SABA) and short-acting muscarinic antagonists (SAMA) are administered for the management of intermittent dyspnea (Quint et al., 2022). Long-acting beta2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) are used for increasing dyspnea. Formoterol, salmeterol, indacaterol, vilanterol and olodaterol are LAMA. SABA, like albuterol, can be administered in the presence or absence of anticholinergics. ASA is the first line of therapy in acute asthma exacerbation (Shin et al., 2021). SABA monotherapy is contraindicated in asthma treatment. Salbutamol, are now coupled with inhaled corticosteroids (ICS) (Marques & Vale, 2023).

The main side effects of bronchodilators include arrhythmias, tremors, and hypokalemia. Caution should be maintained in case of cardiac complications like tachycardia. Coronary heart disease (CHD) is common among patients with COPD-induced emphysema (Parkin et al., 2021). Parkin et al. (2021) conducted a population-based nested case-control study to understand the risk of acute coronary syndrome (ACS) among the users of both LAMA and LABA relative to the users of LAMA. The results showed that relative to the current use of LAMA, current usage of the dual therapy by LABA and LAMA was found to be associated with high risks of ACS. The large sample size of this study helped to increase the credibility and reliability of the data. Parkin et al. (2021) finally concluded that dual yet long-acting bronchodilator therapy rather than LAMA mono-therapy can increase the risk of developing ACS by 50%.

# Relevance to Practice

## Important drug interactions

Navafenterol is a new class of bronchodilators. It is a single-molecule, muscarinic antagonist and beta agonist. It treats emphysema and COPD (Singh et al., 2022). Singh et al. (2022) study aimed to evaluate the efficacy, pharmacokinetics, and safety of the navafenterol versus the placebo for the treatment for emphysema. Singh et al. (2022) conducted a multicentre double-blinded randomised control trial. The study design helped to increase the overall credibility of the research results. The results showed that daily use of the navafenterol is tolerated well by the body, improving the function of the lungs and reducing the severity of the symptoms of emphysema. The results were similar to an established once-daily fixed-dose combination of the bronchodilator (Singh et al., 2022). However, monotherapy of Salbutamol is not recommended for the children with acute exacerbations and thus it is coupled with ipratropium bromide (IB). IB an anticholinergic drug inhibits the parasympathetic nervous system prolonging bronchodilation and giving faster recovery (Marques & Vale, 2023). Salbutamol does not have any significant counter reactions with other drugs (Marques & Vale, 2023).

## Age of the patients and treatment

For athletes and children and people with COPD, who have acute exacerbations of emphysema, for them immediate or prompt dual therapy is recommended (Yamada et al., 2022). The benefit of the prompt vs delayed treatment initiation with the inhaled long-acting bronchodilators in decreasing acute exacerbations of emphysema is unclear (Yamada et al., 2022). To understand the same, Yamada et al. (2022) conducted a retrospective cohort study by analysing patients’ data from the Real world Data database. The results showed that compared with the delayed therapy group (n = 1516), the time to the first exacerbation was prolonged, and the annual rates of the moderate or the severe exacerbations were less among the prompt therapy group. Similarly, the time to the first exacerbation was prolonged, and the annual exacerbation rate (AER) was less in the immediate therapy group in the sub-groups of the patients with chronic bronchitis and emphysema. Thus, this study can be considered the first one to establish the relationship of exacerbation upon initiating the long-acting bronchodilators with 30 days of COPD on set (Yamada et al., 2022).

## Lifestyle interventions

Apart from pharmacological interventions, non-pharmacological intervention like breathing exercise, practising of yoga, mild to moderate walk and complete cessation of smoking are strictly recommended for effective management of emphysema (Marques & Vale, 2023). The experimental study by Kubo et al. (2019) showed that mice exposed to cigarette smoking are prone to develop COPD-induced emphysema, and their condition becomes severe when forced to conduct physical activity. In emphysema, there is abnormal yet permanent dilation of the air spaces and destruction of the alveolar walls under the action of proteinases (Amariei et al., 2019). This result in alveolar damage and a reduction in the surface area of the capillary, decreasing the gas exchange (Amariei et al., 2019). Cigarette smoking also inhibits the secretion of anti-proteolytic enzymes and alveolar macrophages. These genetic polymorphisms play a significant role in the inadequate secretion of antiprotease, contributing to emphysema (Leap et al., 2021). In acinar emphysema, the lung parenchyma secretes alpha one antitrypsin (AAT) that inhibits trypsinize and neutrophil elastase in the lungs, reducing the elasticity of the lungs and reducing the oxygen-carrying capacity (Leap et al., 2021). Thus complete cessation of smoking habit is strictly recommended as lifestyle intervention for emphysema management.

## Presence of co-morbidities and emphysema management

The presence of emphysema did not vary between the group of smokers having lower normal values of lung function and other smokers with no significant variations in lung function. Smokers with emphysema had significantly low BMI in comparison to those who are devoid of emphysema. Obesity increases the BMI, causing breathing trouble and increasing the susceptibility of developing emphysema. Thus BMI needs to be considered during the management of emphysema (Grigsby et al., 2019).

## Nursing management

The nursing management for emphysema must consider the presence of heart disease before the application of bronchodilators and thus must be followed by assessment of BMI and other lifestyle factors like obesity and smoking in order to determine the outcome care. Consideration of these factors will help to design person-centred care plan (Grigsby et al., 2019). The nurse must consider potential benefit/harm ratio of the emphysema treatment intensification provided at the modest benefits of the dual therapy and other lifestyle factor to improve the treatment outcome (Parkin et al., 2021).

# Conclusion

Thus from this essay, it can be summarized that emphysema is common among people who smoke. It is a severe form of COPD. The lungs' alveoli are small air-filled sacs responsible for extracting oxygen from the external atmosphere. In emphysema, the alveoli merge, leading to the formation of a big hole and at the same time, there occurs contraction of the smooth muscles. Contraction of the smooth muscles is an outcome of the hypersensitivity reactions triggered by emphysema. The manifestation of emphysema occurs by increased respiratory distress and laboured breathing. Proper application of the bronchodilators helps relax the smooth muscle cells, thereby helping to improve the oxygen saturation level. However, bronchodilators are not recommended for people having cardiac complications.

# References

Amariei, D. E., Dodia, N., Deepak, J., Hines, S. E., Galvin, J. R., Atamas, S. P., & Todd, N. W. (2019). Combined pulmonary fibrosis and emphysema: pulmonary function testing and a pathophysiology perspective. *Medicina*, *55*(9), 580. <https://doi.org/10.3390/medicina55090580>

Barjaktarevic, I. Z., Buhr, R. G., Wang, X., Hu, S., Couper, D., Anderson, W., ... & NHLBI SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS). (2019). Clinical significance of bronchodilator responsiveness evaluated by forced vital capacity in COPD: SPIROMICS cohort analysis. *International journal of chronic obstructive pulmonary disease*, 2927-2938. DOI: 10.1183/13993003.00561-2019

Basil, M. C., Katzen, J., Engler, A. E., Guo, M., Herriges, M. J., Kathiriya, J. J., ... & Morrisey, E. E. (2020). The cellular and physiological basis for lung repair and regeneration: past, present, and future. *Cell Stem Cell*, *26*(4), 482-502. Available at: <https://www.cell.com/cell-stem-cell/pdf/S1934-5909(20)30101-6.pdf>

Grigsby, M. R., Siddharthan, T., Pollard, S. L., Chowdhury, M., Rubinstein, A., Miranda, J. J., ... & Checkley, W. (2019). Low body mass index is associated with higher odds of COPD and lower lung function in low-and middle-income countries. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *16*(1), 58-65. https://doi.org/10.1080/15412555.2019.1589443

Humphries, S. M., Notary, A. M., Centeno, J. P., Strand, M. J., Crapo, J. D., Silverman, E. K., ... & Genetic Epidemiology of COPD (COPDGene) Investigators. (2020). Deep learning enables automatic classification of emphysema pattern at CT. *Radiology*, *294*(2), 434-444. https://doi.org/10.1148/radiol.2019191022

Kubo, H., Asai, K., Kojima, K., Sugitani, A., Kyomoto, Y., Okamoto, A., ... & Kawaguchi, T. (2019). Exercise ameliorates emphysema of cigarette smoke-induced COPD in mice through the exercise-irisin-Nrf2 axis. *International Journal of Chronic Obstructive Pulmonary Disease*, 2507-2516. Available at: <https://www.tandfonline.com/doi/full/10.2147/COPD.S226623>

Leap, J., Arshad, O., Cheema, T., & Balaan, M. (2021). Pathophysiology of COPD. *Critical care nursing quarterly*, *44*(1), 2-8. *DOI:*10.1097/CNQ.0000000000000334

Marques, L., & Vale, N. (2023). Unraveling the Impact of Salbutamol Polytherapy: Clinically Relevant Drug Interactions. *Future Pharmacology*, *3*(1), 296-316. [**https://doi.org/10.3390/futurepharmacol3010019**](https://doi.org/10.3390/futurepharmacol3010019)

Parkin, L., Williams, S., Sharples, K., Barson, D., Horsburgh, S., Jackson, R., ... & Dummer, J. (2021). Dual versus single long‐acting bronchodilator use could raise acute coronary syndrome risk by over 50%: A population‐based nested case–control study. *Journal of Internal Medicine*, *290*(5), 1028-1038. <https://doi.org/10.1111/joim.13348>

Powers, K. A., & Dhamoon, A. S. (2019). Physiology, pulmonary ventilation and perfusion. *Europe PMC.* Available at: <https://europepmc.org/article/NBK/nbk539907>

### Quint, J. K., Arnetorp, S., Kocks, J. W., Kupczyk, M., Nuevo, J., Plaza, V., ... & Weesie, Y. M. (2022). Short-acting beta-2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and North America. *The Journal of Allergy and Clinical Immunology: In Practice*, *10*(9), 2297-2309. <https://doi.org/10.1016/j.jaip.2022.02.047>

Rodrigues, S. D. O., Cunha, C. M. C. D., Soares, G. M. V., Silva, P. L., Silva, A. R., & Gonçalves-de-Albuquerque, C. F. (2021). Mechanisms, pathophysiology and currently proposed treatments of chronic obstructive pulmonary disease. *Pharmaceuticals*, *14*(10), 979. <https://doi.org/10.3390/ph14100979>

Santus, P., Pecchiari, M., Tursi, F., Valenti, V., Saad, M., & Radovanovic, D. (2019). The airways’ mechanical stress in lung disease: implications for COPD pathophysiology and treatment evaluation. *Canadian Respiratory Journal*, *2019*. <https://doi.org/10.1155/2019/3546056>

### Shin, S. H., Shin, S., Im, Y., Lee, G., Jeong, B. H., Lee, K., ... & Park, H. Y. (2021). Effect of perioperative bronchodilator therapy on postoperative pulmonary function among lung cancer patients with COPD. *Scientific Reports*, *11*(1), 8359. <https://doi.org/10.1038/s41598-021-86791-1>

Singh, D., Beier, J., Astbury, C., Belvisi, M. G., Da Silva, C. A., Jauhiainen, A., ... & Psallidas, I. (2022). The novel bronchodilator navafenterol: a phase 2a, multicentre, randomised, double-blind, placebo-controlled crossover trial in COPD. *European Respiratory Journal*, *59*(4). DOI: 10.1183/13993003.00972-2021

Yamada, H., Matsumoto, I., Makita, N., Arita, Y., Hayashi, N., Mitsuoka, K., ... & Hizawa, N. (2022). Effect of timing of bronchodilator therapy initiation on exacerbations in patients with chronic obstructive pulmonary disease: a retrospective cohort study. *Respiratory Research*, *23*(1), 255. <https://doi.org/10.1186/s12931-022-02184-6>