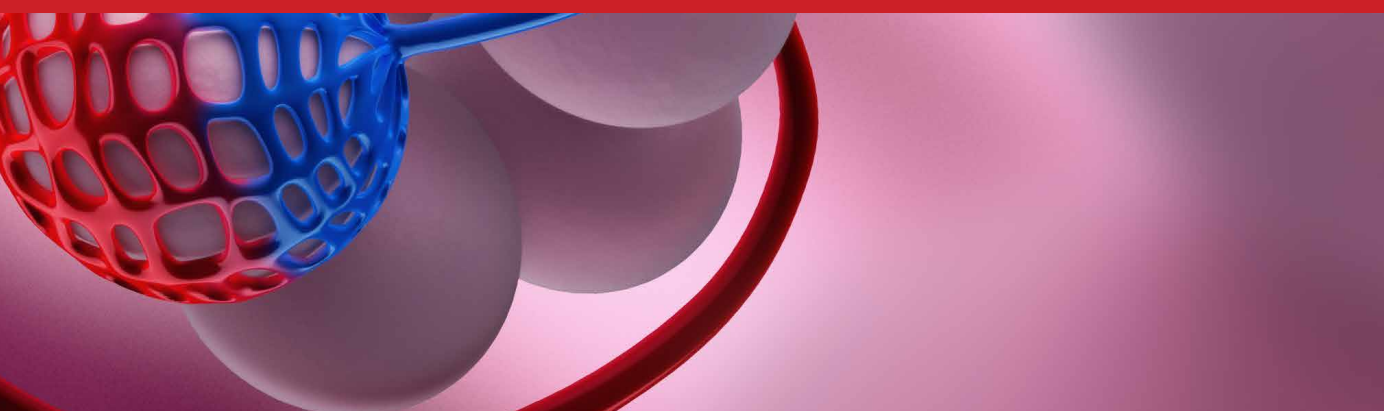


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Chronic Obstructive Pulmonary Disease

Contemporary and Consummate Management of a Systemic Disorder

Edited by Kian Chung Ong



Chronic Obstructive Pulmonary Disease - Contemporary and Consummate Management of a Systemic Disorder

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Meet the editor



Dr. Kian Chung Ong is a specialist in Respiratory and Intensive Care Medicine with 25 years of clinical experience. He is currently the medical director of the Chestmed Clinic at Mount Elizabeth Medical Centre, Singapore. Dr. Ong has authored over 50 scientific papers, 10 book chapters, and served as the editor of six open-access textbooks relevant to Respiratory Medicine. He has been a member of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Assembly since its establishment in 2000. He is also the founder and current president of the Chronic Obstructive Pulmonary Disease Association (Singapore). Beyond the clinical requirements of private specialist practice, Dr. Ong is committed to conducting translational research in lung disease in collaboration with tertiary academic institutions in Singapore.

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Preface

Chronic Obstructive Pulmonary Disease (COPD) is a common and complex disorder that requires frequent updates of one's knowledge base. The yearly updates to the guidelines for the management of COPD, issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) since its inception at the turn of the century, are a testament to the need for ongoing, informed updates in confronting the disease. By combining the knowledge and experience of professionals from diverse backgrounds worldwide, and presenting information rapidly in a peer-reviewed format, this compendium of articles aims to contribute to the current understanding of COPD.

The best place to start a book on COPD is with the patient. It is increasingly accepted that social participation in healthcare is essential for improving healthcare delivery.

Chapter 2 is a narrative review chapter that describes the phenotypes in COPD, particularly those associated with eosinophilic airway inflammation. Although the COPD phenotypes described in the literature are numerous, the author has chosen to focus on phenotypes characterized by sputum and peripheral eosinophilia, as they are clinically relevant and helpful biomarkers, as well as treatable traits of COPD. The information provided is up to date and helpful in clinical practice.

This is followed by Chapter 3, a truly state-of-the-art overview of in vitro models of COPD. This is a highly specialized field of research, and the authors have excelled at condensing the vast, complex knowledge base into a concise digest that both basic scientists and busy clinicians will appreciate.

Chapter 4 presents an exquisite proof-of-concept study demonstrating the novel technology's ability to non-invasively detect cerebral hypoxemia induced by exercise in patients with COPD. The utility of such a device extends beyond exercise rehabilitation in these patients.

Depressive and psychosocial factors associated with COPD are clinically important, and recognizing these factors and using appropriate instruments to accurately measure their impact on the patient and the disease are the focus of Chapter 5.

In Chapter 6, a review of observational data from the COVID-19 pandemic presents an interesting case for advocating ongoing infection-control measures to reduce hospitalizations among patients with COPD and those at high risk of developing community-acquired pneumonia. The final chapter points toward the future. The use of artificial intelligence is transforming the world in many ways, and an interesting additional utility is the development of diagnostic and therapeutic algorithms for pulmonary hypertension, a dreaded complication in COPD.

I hope this book will serve as a valuable resource for all who share an academic interest in progressive scientific research and best practices in COPD. Last but not least,

I would like to express my appreciation to the book chapter authors and our author service manager, Laura Divic, for their contributions and assistance in making this publication a reality.

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Singapore

Chapter 1

Introductory Chapter: Patient Advocacy in Chronic Obstructive Pulmonary Disease and Pneumonia

Kian Chung Ong

1. Introduction

Patient advocacy (PA) is a process in healthcare, which aims to ensure that patients and their families receive the best possible care and support. Patient advocates are usually patients, their families, or caregivers, and these individuals may either be lay volunteers or healthcare professionals. PA may also be provided by organizations such as support groups and welfare organizations. Key aspects of PA are: (1) empowering patients to understand their rights and to make informed decisions about their care through education and support; (2) improving healthcare access by working to overcome barriers of care and ensuring equitable access to services; (3) fostering communication and collaboration by mediating disputes between patients and healthcare providers; and (4) participating in research and policy formulation via the sharing of patient perspectives and lived experiences.

The Sustainable Development Goal set by the World Health Organization (WHO) for "responsive, inclusive, participatory and representative decision-making at all levels" is best served by encouraging social participation in healthcare [1]. Social participation should be promoted across the healthcare spectrum. This requires PA groups to engage the health system at all levels – the overall health system level to effect civil society participation in reimbursement and inclusion discussions; the service provider (medical schools, primary care clinics, hospitals) levels to help improve quality of care; and the patient or consumer level to raise awareness of diseases and patients' rights.

The term "double burden of disease" has often been used to refer to a situation where a population is simultaneously affected by two distinct types of health issues: communicable diseases (often associated with poverty and inadequate healthcare infrastructure) and non-communicable diseases (typically associated with affluence and lifestyle factors). This concept is particularly relevant in regions undergoing rapid socioeconomic transitions where funding is limited and usually over-focused on, or urgently diverted to infectious disease, as was the case during the recent coronavirus disease 2019 (COVID-19) pandemic. Diseases for which PA are considered important, if not essential, comprise common non-communicable diseases such as diabetes, heart disease, chronic obstructive pulmonary disease (COPD), cancers, and arthritis, which are resource-intensive; rare and complex genetic or autoimmune diseases with limited access to specialized care; and those facing stigmatization and discrimination, e.g. HIV/AIDS, and mental disorders. Nonetheless, among patients

with common and serious acute infection, the need for advocacy also exists, for which there is no greater pressing need for action than in confronting community-acquired pneumonia, which was the single, biggest infectious killer of adults and children in 2021. Pneumonia claimed the lives of 2.2 million, including 502,000 children, and COVID-19 killed an additional 10 million. Together, they caused more deaths than any other illness, including heart disease [2]. As highlighted during COVID-19, among patients who develop pneumonia, a lack of awareness and agreement between patients and their care-providers can lead to delay and disparity in urgent resource allocation, thus vitiating treatment programs.

This article discusses issues related to PA, leveling at patients afflicted by acute pneumonia and their care-providers. In particular, the rights and responsibilities of patients with pneumonia and certain ethical issues related to the urgent treatment of the condition are explored.

2. The development of a COPD patient charter

PA typically begins with raising awareness of medical conditions among patients and their families. This is important because patients, especially those of lower educational backgrounds, are the weaker party in a physician-patient dyad with asymmetric information, and patients' informed decision-making and autonomy can quite easily be compromised or circumvented. The asymmetric information levels between patients and their care-providers are often the cause of limitations in autonomy and informed consent.

A group of global patient advocates has previously developed a patient charter to set a standard of care quality that patients living with COPD should expect, to raise awareness and to improve outcomes [3]. A patient charter is described as a document outlining the rights and responsibilities of patients in a healthcare setting, with the overall objective of promoting patient-centered care. To date and the author's knowledge, no such document outlining the rights and expectations of individuals diagnosed with pneumonia exists, although pneumonia is a respiratory condition closely associated with COPD and surpassing the latter in prevalence, mortality, and disease burden. A pneumonia patient charter should outline the rights, responsibilities, and expectations for individuals with pneumonia, ensuring they receive appropriate care and support throughout their illness. Such basic issues need not be addressed *ab initio*, as knowledge gained in the formulation of the COPD patient charter are applicable to patients with pneumonia. Fundamental rights of patients with pneumonia include the following: Patients have the right to understand their diagnosis, treatment options, potential risks and benefits of treatment, as well as prognosis of their condition. Patients' personal information and information about their condition are confidential and to be shared with authorized personnel only. Patients have the right to participate in treatment decisions and should be actively involved in making decisions about their care, including participating in research. Patients have the right to access quality care, including prompt diagnosis, effective treatment, and follow-up support. Patients have the right to be treated with respect, empathy, and dignity by their healthcare workers, regardless of their age, gender, race, religion, or other personal characteristics. Patients have the right to be informed about the costs of their care in advance.

Conversely, the responsibilities of all patients include the following. Patients should seek prompt medical attention if they suspect they have pneumonia. Patients should

adhere to their prescribed treatment plan, including taking medications as directed, following dietary and lifestyle recommendations, and attending follow-up appointments. Patients should communicate openly with their healthcare providers about their concerns, questions, and requirements, and advocate for their needs and rights.

Based on these rights and responsibilities, patients with pneumonia can expect healthcare providers to provide timely and appropriate medical care, to be responsive to their needs, and to communicate effectively with them. They can also expect to receive support from their healthcare team, family, and friends throughout their illness, including emotional support, practical assistance, and access to resources. While recovery periods may vary, patients can expect prompt and effective treatment to lead to improving symptoms and return to their normal condition.

3. Toward the development of a pneumonia patient charter

Borrowing from the key principles of the foregoing COPD patient charter [3], the following are additional recommendations for consideration in developing a patient charter for patients with pneumonia:

1. Patients and their carers should be educated to recognize the symptoms of pneumonia and seek early medical attention, and healthcare providers should have access to the right tools and instruments to make an accurate diagnosis.

2. Patients should receive personalized management plans with regular, proactive reviews and adjustment of treatment to ensure maximum potential of recovery and return to normal activities.

3. National policymakers and healthcare professionals should recognize the emergence of new pathogens and infectious disease outbreaks and advice or implement measures to limit contagion within the community to prevent or reduce the incidence of community-acquired pneumonia.

4. All patients with pneumonia should have access to specialist care. Utilizing tools such as digital health technology can improve issues in triage of patients especially during disease outbreaks and accessing specialist care in remote areas.

5. Healthcare professionals, patients, and the public should be educated on the disease process of respiratory infections and pneumonia to reduce the associated stigma, encourage patients to seek help, and lessen nihilism among healthcare workers.

Beyond these general recommendations, several specific aspects of pneumonia care require consideration among patient advocates and healthcare providers as they also impact patients' rights. The Every Breath Counts Coalition is an international confederacy that aims to reduce the number of children and adults dying from pneumonia by 2030 by closing critical gaps in prevention, diagnosis, and treatment of pneumonia across the globe [2]. Endeavors to overcome the critical challenges to the current management of pneumonia that are highlighted by the coalition must form the major milestones of PA efforts and be considered carefully in the development of a patient charter on pneumonia. In prevention, the issues identified are as follows.

First, regarding vaccination, the availability and access to currently available and effective vaccines to people, especially children, are limited in many countries, and the development of vaccines that can prevent viral and bacterial causes of pneumonia are important in the fight against pneumonia. Second, air pollution is the leading risk factor for death from pneumonia across all ages, with almost a third of all pneumonia deaths worldwide attributable to polluted air. While global pneumonia deaths from indoor (household) air pollution have declined since 2010, they are alarmingly rising due to outdoor air pollution, especially in Asia. Third, malnutrition is the leading risk factor for pneumonia deaths in children, and this will militate against vaccinations and other efforts to reduce childhood mortality unless malnutrition is identified and treated early in life.

For the diagnosis of pneumonia, timely care-seeking from qualified healthcare is critical, but this is not possible in many countries, especially for children. The Every Breath Counts Coalition has identified using pulse oximetry and new technologies like lung ultrasound and artificial intelligence to transform the diagnosis of pneumonia in low-resource settings, as these may have benefits over traditional X-rays. In particular, pulse oximetry is a simple, non-invasive, inexpensive, and very effective tool that measures oxygen saturation in the blood. Pulse oximeters can detect hypoxemia in patients relatively accurately, thus providing an objective evaluation that helps to quickly identify the presence of pneumonia in patients with symptoms of acute respiratory infection, thus segregating patients with lower respiratory tract infections from those without. Hypoxemia that complicates pneumonia can be life threatening and it is essential to identify the former as early as possible so that oxygen supplementation can be provided. In spite of their lifesaving potential, pulse oximeters are not widely available in healthcare facilities in low-resource settings and not widely used in primary care settings. Also, the transcutaneous oxygen saturation measurement using pulse oximeters is known to underestimate blood oxygen saturation in patients with darker skin pigmentation. In spite of these shortcomings, the use of pulse oximetry should be encouraged as it is a helpful aid in diagnosis and treatment of patients with pneumonia.

Pertaining to the issue of treatment, the availability of safe, affordable, quality treatments for pneumonia is particularly limited in low-resource settings. Contrariwise, overuse of antibiotics in certain countries has led to concerns of a "pandemic of antimicrobial resistance". Antimicrobial resistance is a major global health and socioeconomic crisis. Indiscriminate and inappropriate overuse of antimicrobials increases the prevalence of drug-resistant pathogens and the treatment costs and mortality of community-acquired as well as nosocomial pneumonias. Overuse of antimicrobials does not just negatively impact humans but also animal health, food production, and the environment. Education and advocacy to raise public and stakeholder awareness on stewardship of antimicrobials are key strategies to counter this problem. Strong political will, advocacy, and accountability are needed at all levels of the healthcare system to counter antimicrobial resistance before it is too late. The use of supplemental oxygen is lifesaving for patients with pneumonia who are hypoxemic. Before the COVID pandemic, many countries faced a shortage of medical-grade oxygen but since more than 100 nations have received oxygen supplies during the pandemic, now is the time to ensure the availability of medical oxygen to save lives in all countries [4]. Recognizing the long-standing lack of access to medical oxygen that was crudely highlighted during the recent pandemic, the Lancet Global Health Commission on Medical Oxygen Security was established in September 2022 to develop and recommend concrete actions for governments, industry, global

health agencies, healthcare workforce, donors, and researchers. Governments have also committed under the WHO Access to Medical Oxygen Resolution to develop costed, national plans to guarantee access to medical oxygen in their health systems. (Currently less than 30 member countries have such plans, and medical oxygen remains largely omitted from global and national emergency pandemic preparedness). As for the medical industry, increases in both domestic and international funding to strengthen national medical oxygen systems are critical and donors should contribute to the US$4 billion resource mobilization target of the Global Oxygen Alliance (GO_2AL) between 2025 and 2030. While these developments are taking place at international levels, a patient charter on pneumonia should ride on the evidence and recommendations provided by these global agencies to advocate for the patients' right to medical oxygen therapy, which is without substitute, and to contend that no patient should die for the lack of it. Specifically, the Every Breath Counts Coalition has called on all national governments to ensure that pulse oximetry and oxygen are provided free at the point-of-care, especially for patients most at risk of death from hypoxemia. Pulse oximetry and oxygen are also to be made available in primary health facilities and during transport of hypoxemic patients to higher-level care facilities. However, to date, the inequities in access to free medical oxygen persist, so in addition to health system level advocacy, there is much to be done in PA among healthcare providers and consumers.

Another issue related to the treatment of pneumonia has also been emphasized by the Every Breath Counts Coalition [2] – with more than 400 million adults and children contracting pneumonia each year, the costs of treatment can be crippling and catastrophic if no universal health coverage is available, and individuals and families are forced to pay out-of-pocket for healthcare. Recognizing the fact that reducing pneumonia deaths will depend on how effectively governments can reduce the costs of treatment, the WHO and World Bank continue to track universal health coverage in countries with the inclusion of an indicator on pneumonia care-seeking [5]. The WHO Sustainable Development Goal 3.8 aims to achieve universal health coverage, including financial risk protection, access to quality essential healthcare services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all by 2030. However, the latest figures show dismal progress toward this goal. For unknown reasons, the South-East Asia Region continued to be the second worst-performing region in the world on catastrophic out-of-pocket health spending. PA on the consumer and care-provider levels should emphasize universal health coverage as the means that all people have access to the full range of quality health services they need, when and where they need them, without financial hardship. For patients with pneumonia, coverage for the full continuum of essential health services is required to improve survival rates and reduce morbidity disability.

By outlining the rights, responsibilities, and expectations, and tackling issues pertinent to the disease across the world, PA with the establishment of a pneumonia patient charter can help ensure that patients receive the best possible care and support throughout their illness.

4. Ethical considerations at end-of-life care

With the high mortality portended by pneumonia and COPD throughout the world, a discussion on PA for sufferers of these diseases would not be complete without a consideration of end-of-life care and the ethical principles associated

with it. The situations where difficulty in decision-making regarding end-of-life care is encountered include the following: withholding or withdrawing treatment, cardiopulmonary resuscitation, mechanical ventilation, artificial nutrition and hydration, terminal sedation, euthanasia, and physician-assisted suicide. Decision-making in such situations is challenging as all parties involved in the clinical ethical decision-making process – patients, family members, and society should have their rights and dignity protected. Ethically, the patient, rather than the family, proxy, or physician, should make the decisions about limiting treatment or treatments, but patients may not have the ability or will to do so, and the family members may not all agree. In such scenarios, healthcare providers may rely on the universal ethical principles of autonomy, beneficence, non-maleficence, and justice as outlined above, to guide their decision-making and actions. A fifth ethical principle – fidelity may also be helpful [6]. The fidelity principle requires physicians to be honest with their dying patients about their prognosis and likely consequences of patients' disease. Albeit truth telling is fundamental to respecting autonomy, here again some patients may refuse information about their disease, and the desire for knowledge often decreases as they approach the end of their lives. The attending care-providers thus need to be sensitive and skilled in presenting patients with as much accurate information as the patients want. Open communication and shared decision-making between healthcare providers, patients, and their families can help resolve the ethical dilemmas at end-of-life care.

5. Conclusions

In summary, PA for COPD and pneumonia care entails multiple perspectives and propositions as these common illnesses afflict numerous individuals of diverse backgrounds in different countries around the globe. Social participation in healthcare of high burden diseases such as COPD and respiratory infections should be promoted and aimed at multiple levels in the healthcare spectrum to maximize its impact. On a global scale, the standard of pneumonia care is almost universally below par, and coordinated empowerment and advocacy is required to attain international health targets. At the levels of the consumer and the care-provider, the formulation of a patient charter that emphasizes the essential care elements for a patient suffering from pneumonia will help to affirm the patient's rights and provide expectations of a care plan. Patient advocates can also assist in facilitating shared decisions for managing COPD and pneumonia, and in mediating the ethical challenges encountered in critical care and in crisis resource planning.

Conflict of interest

The author declares no conflict of interest.

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Chapter 2

Chronic Obstructive Pulmonary Disease (COPD): Phenotypes and Biological Players

Lokesh Verma, Atul Soni and Govind Desai

Abstract

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms such as dyspnea, cough, sputum production, and exacerbations, resulting from airway and alveolar abnormalities leading to persistent airflow obstruction. This chapter explores COPD phenotypes, traditionally categorized as "pink puffers" (emphysema-dominant) and "blue bloaters" (chronic bronchitis-dominant), and the role of eosinophils in disease pathogenesis. It discusses the complexity of asthma-COPD overlap (ACO), the significance of biomarkers like blood and sputum eosinophil counts, and fractional exhaled nitric oxide (FeNO) in identifying type 2 inflammation. Recent evidence on the efficacy of inhaled corticosteroids (ICS) and biologics (e.g., mepolizumab, benralizumab, dupilumab) in eosinophilic COPD is reviewed, highlighting their impact on exacerbation rates and lung function. The chapter emphasizes the need for precise diagnostic criteria and personalized treatment strategies to address the diverse clinical presentations of COPD.

Keywords: COPD, eosinophilia, phenotypes, asthma-COPD overlap, biologics, type 2 inflammation, biomarkers, corticosteroids

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health concern defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 as a heterogeneous condition characterized by chronic respiratory symptoms, including dyspnea, cough, sputum production, and exacerbations, due to airway (bronchitis, bronchiolitis) and/or alveolar (emphysema) abnormalities causing persistent, often progressive, airflow obstruction [1]. Historically, COPD phenotypes were described as "pink puffers" (emphysema-dominant) and "blue bloaters" (chronic bronchitis-dominant), each presenting distinct clinical characteristics (**Table 1**). Understanding the role of biological players—exposome, genome, endotypes, phenotypes, biomarkers, and treatable traits—is critical for tailoring effective therapeutic strategies. This chapter examines COPD

Pink puffer	Blue bloater
More emphysema	Higher BMI, obesity
Barrel chest	More chronic bronchitis
More dyspnea	More severe pulmonary hypertension
Less cough	More hypercapnic response
Mild pulmonary hypertension	Less hypercapnic response

Table 1.
Characteristics of COPD phenotypes.

phenotypes, the role of eosinophilia, the complexities of asthma-COPD overlap (ACO), and the therapeutic potential of corticosteroids and biologics in managing eosinophilic COPD [2–5].

2. COPD phenotypes and clinical presentations

COPD is a complex disease with varied clinical presentations, as illustrated by four clinical cases (**Table 2**). These cases highlight the challenge of compartmentalizing COPD due to overlapping factors such as smoking history, occupational exposures, comorbidities, and eosinophil counts.

These cases demonstrate the heterogeneity of COPD, with eosinophil counts exceeding the 2% threshold, raising questions about asthma-COPD overlap (ACO) or eosinophilic COPD.

3. Eosinophilia in COPD

3.1 Prevalence of eosinophilia

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study reported that 37.4% of COPD patients had persistently elevated eosinophil counts (≥2%) at all visits, while 49% had variable counts [6]. Another study found that 87% of COPD patients had blood eosinophil counts consistently above 100 cells/μL, with 51 and 19% above 150 and 300 cells/μL, respectively

Feature	Case 1	Case 2	Case 3	Case 4
Age/gender	65/M	67/F	63/F	64/F
Smoking history	80-pack-year	46-pack-year (quit 4y)	45-pack-year (quit 6 m)	25-pack-year (quit 3y)
Eosinophils	200	700	21%	500
CT findings	No emphysema	Extensive	No emphysema	Extensive
PFT	44% reversibility		No reversibility	Strong reversibility

Table 2.
Clinical case presentations for COPD.

[7]. Patients with a history of asthma exhibited significantly higher eosinophil counts, suggesting a potential overlap with ACO [6, 7].

3.2 Eosinophils and exacerbations

Emerging data link higher blood eosinophil counts to an increased risk of COPD exacerbations [8–10]. However, a real-life cohort study found no significant differences in prognosis or lung function between patients with higher versus lower eosinophil counts at various thresholds (2, 3, 4%) [11]. Another study reported that persistent eosinophil counts ≥300 cells/μL over 2 years were not associated with exacerbations but correlated with better survival [12]. These inconsistencies highlight the need for standardized outcome measures.

3.3 Eosinophils as a biomarker for steroid response

Blood eosinophil counts ≥300 cells/μL are a promising biomarker for identifying COPD patients likely to benefit from corticosteroid therapy during exacerbations [13]. The GOLD 2025 report recommends ICS for Group E patients with ≥2 moderate exacerbations or ≥ 1 severe exacerbation, particularly if eosinophil counts are ≥300 cells/μL [1]. However, the Fluticasone Salmeterol on COPD Exacerbations (FLAME) trial suggests that eosinophil counts may not reliably guide the choice between LABA/ICS and LABA/LAMA regimens, necessitating further research [14].

4. Asthma-COPD overlap (ACO)

The GOLD 2025 report no longer uses the term ACO, recognizing asthma and COPD as distinct disorders that may coexist with the shared treatable traits, such as elevated eosinophil counts and bronchodilator responsiveness [1]. ACO is characterized by features of both asthma (e.g., reversibility) and COPD (e.g., fixed airflow obstruction) [15]. The absence of specific diagnostic criteria complicates determining its global prevalence, but higher eosinophil counts are consistently observed in these patients [15, 16].

5. Biomarkers in eosinophilic COPD

5.1 Blood and sputum eosinophil counts

Sputum eosinophil counts (≥1.25%) are a better biomarker than blood eosinophil counts (≥200 cells/μL) for identifying severe COPD, frequent exacerbations, and emphysema, as shown in the SPIROMICS study [17]. However, sputum eosinophil measurement is less practical than blood tests. The correlation between blood and sputum eosinophil counts is weaker in COPD compared to asthma [18].

5.2 Fractional exhaled nitric oxide (FeNO)

The BOREAS trial demonstrated that dupilumab significantly reduced FeNO levels (−28.6 ppb vs. -6.9 ppb for placebo) over 52 weeks, suggesting FeNO as a practical biomarker for type 2 inflammation in COPD [19]. FeNO may be more accessible than sputum eosinophil counts for clinical use.

6. Treatment of eosinophilic COPD

6.1 Inhaled corticosteroids (ICS)

The GOLD 2025 report recommends initiating ICS in combination with LABA and LAMA for patients with eosinophil counts ≥300 cells/μL and frequent exacerbations [1]. ICS benefits are observed at counts ≥100 cells/μL, with greater efficacy at higher counts, though severe disease increases pneumonia risk [20]. Triple therapy (LABA/LAMA/ICS) is preferred over LAMA/ICS [20].

6.2 Biologics

Biologics targeting type 2 inflammation, particularly IL-5, IL-4, and IL-13 pathways, show promise in eosinophilic COPD. Key trials include the following:

- Mepolizumab (METREX and METREO): Reduced exacerbation rates by 18–19% in patients with eosinophil counts ≥150 cells/μL, with no significant improvement in symptom scores [21, 22].
- Benralizumab (GALATHEA and TERRANOVA): Non-significant reduction in exacerbation rates but improved lung function; reduced severe exacerbations requiring hospitalization by 63–68% in patients with eosinophil counts ≥220 cells/μL [22, 23].
- Dupilumab (BOREAS): Reduced exacerbation rates (rate ratio 0.70), improved lung function (160 mL vs. 77 mL in FEV1), and enhanced quality of life in patients with eosinophil counts ≥300 cells/μL [19].

Study component	Mepolizumab	Benralizumab	Dupilumab
Eosinophil criteria	≥150 cells/μL	≥300 cells/μL	≥200–300 cells/μL
Exacerbation rate	↓18%	No significant reduction	↓30%
Lung function	No change	Improved	↑ FEV1 by 160 mL
Symptoms	No difference	Improved	Improved

Table 3.
Key highlights from trials of anti-IL therapies.

Treatment	Studies; participants	RR (95% CI)	Certainty	Results
Mepolizumab 100 mg	2; n = 911	0.81 (0.71–0.93)	High	19% reduction in exacerbations
Mepolizumab 300 mg	1; n = 451	0.86 (0.70–1.06)	Moderate	14% reduction in exacerbations
Benralizumab 100 mg	2; n = 1512	0.63 (0.49–0.81)	High	37% reduction in severe exacerbations
Benralizumab 10 mg	1; n = 765	0.68 (0.49–0.94)	Moderate	32% reduction in severe exacerbations

Table 4.
Meta-analysis results on anti-IL-5 therapies.

A Cochrane meta-analysis confirmed that mepolizumab and benralizumab reduce moderate-to-severe exacerbations in eosinophilic COPD [22]. Dupilumab's inhibition of IL-4/IL-13 also addresses mucus secretion and airway remodeling, suggesting broader therapeutic potential (**Tables 3** and **4**) [19].

7. Conclusion

COPD is a heterogeneous disease with diverse phenotypes and biological mechanisms. Eosinophilia, a key feature in some patients, is associated with exacerbations and responsiveness to corticosteroids and biologics. Blood eosinophil counts ≥300 cells/μL guide ICS therapy, while sputum eosinophil counts and FeNO offer additional insights into type 2 inflammation. Biologics like mepolizumab, benralizumab, and dupilumab show promise in reducing exacerbations and improving lung function in eosinophilic COPD. However, the lack of specific diagnostic criteria for ACO and variability in eosinophil-related outcomes underscore the need for further research to refine the personalized treatment approaches.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 3

In Vitro Models of Chronic Obstructive Pulmonary Disease (COPD)

Anushka Jain, Laxmi, Sanjita Das and Gyas Khan

Abstract

Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity and mortality worldwide, placing an enormous burden on healthcare facilities and society. This chapter thoroughly investigates the creative application of *in vitro* models to elucidate the intricate etiology of COPD and promote the identification of novel therapeutic approaches. Despite their convenience, traditional two-dimensional models that use immortalized cell lines frequently fall short of accurately simulating the complex milieu of human lung tissue, which makes it difficult to anticipate how a disease will proceed and how well a medication will work. Primary human airway epithelial cells, especially when cultivated at the air-liquid interface, provide a more physiologically appropriate model that closely resembles the properties and interactions of human respiratory epithelium. Developing organoid models capable of mimicking the structure and function of the lung in three dimensions has been an important advancement in the study of COPD. These organoids have many potential applications, including improved disease modeling, individualized treatment, and high-throughput drug screening. Recent advancements in organ-on-chip and bioprinting technology have enhanced these models, allowing for more accurate replication of human lung physiology. The integration of *in vitro, in vivo*, and *in silico* approaches is highlighted as a holistic approach to enhancing our comprehension of COPD's intricate biology and refining therapeutic strategies. Notwithstanding considerable advancements, obstacles remain in precisely replicating human disease characteristics and converting preclinical discoveries into clinical use. This chapter emphasizes the essential importance of ongoing innovation of COPD modeling, facilitating the development of more effective, targeted, and personalized therapies.

Keywords: *In vivo*, *In vitro*, pulmonary, cell lines, air-liquid Interface, cytokine, chemokine

1. Introduction

According to WHO estimates, COPD ranks as the third leading cause of death globally, with yearly costs over $100 billion [1]. COPD is a progressive disease

caused by inhaling harmful particles or gases. The main etiological factors of COPD are tobacco use and exposure to other pollutants [2]. It is a heterogeneous disorder characterized by diverse contributions from airway obstruction and lung parenchymal degradation (emphysema) [3]. COPD symptoms may encompass persistent or progressively increasing shortness of breath, chronic cough that yields mucus, chest congestion, and profound fatigue. In many instances, a persistent cough, with or without mucus secretion, may be irregular and can lead to the onset of airflow restriction by several years [1]. An acute inflammatory reaction to these foreign molecules eliminates pathogens to prevent additional harm, although this response lacks memory. This inflammation and remodeling frequently impact both the lung parenchyma and the air passages. COPD patients exhibit elevated levels of neutrophils, macrophages, and T lymphocytes (CD8>CD4) in their pulmonary tissue. These inflammatory cells secrete several cytokines and chemotactic substances that exacerbate inflammation [4]. Oxidants originating from cigarette smoke and emitted by inflammatory leukocytes may contribute to the excessive production of mucin through the activation of the MUC5AC gene [5]. The pulmonary cholinergic system also contributes the structural identified in the airways of COPD patients. Collagen synthesis and fibroblast proliferation are both enhanced by activating M2 and M3 receptors in cultured fibroblast cells [6]. A notable pathophysiological feature is the pronounced apoptosis of alveoli and bronchiolar epithelial cells, in conjunction with pulmonary capillaries, which are evident in histological analyses of emphysema, as well as in biological characteristics such as reduced alveolar surface area for the imbalance between ventilation and perfusion and gas exchange. Moreover, emphysema diminishes lung elastic recoil pressure, hence reducing the generating pressure for expiration through restricted, inadequately maintained airways characterized by significantly increased airflow resistance [7]. Hyperinflated lungs, often known as air trapping, are a hallmark of the pathophysiology of COPD. COPD is often linked to increased residual volume (RV), total lung capacity (TLC), functional residual capacity (FRC), and a heightened RV/TLC ratio [5]. Although progress has been made in the therapy of COPD during the last two decades, it primarily depends on bronchodilators and corticosteroids [8]. The objectives of COPD treatment encompass acknowledging the influence of symptoms and exacerbations on the lives of patients within the paradigm of effective patient-centered care [9]. Complex co-culture models are crucial for simulating the *in vivo* circumstances of the lung and elucidating the pathways and mediators implicated in compromised epithelial-fibroblast relations in COPD [10]. *In vitro* models that accurately replicate the pulmonary environment are becoming increasingly significant due to ethical concerns with animal experimentation, inadequate translation to human pathology, extended time to market, and elevated attrition rates in clinical trials [11]. Several *in vitro* models have been used as the foundation for both long-standing and novel advancements in the research of chronic respiratory disorders over the years. This encompasses cell lines, gene expression techniques, siRNA sequencing, cytometry, and culture procedures, and serum/sputum biomarkers that help clarify the molecular underpinnings of various diseases and reveal new diagnostic and therapy alternatives [12]. *In vitro* modeling of COPD facilitates the examination of the mechanisms behind its development by enabling direct assessment of cellular responses to cigarette smoke, oxidants, fine particles, and proteolytic enzymes. In addition to identifying novel targets for therapeutic interventions, *in vitro* exposure models provide a comprehensive assessment of

the pharmacological efficacy of both existing and emerging medicines for COPD. Nonetheless, the drawback of using pharmacotherapies *in vitro* is that the drug concentrations utilized may frequently exceed those that would be attained by the relevant cell type *in vivo* when administering aerosolized pharmacotherapies. *In vivo* therapies frequently exhibit inconsistent distribution to the lungs due to variations in particle deposition and the metabolism of pharmacotherapies [13]. This chapter explores the various *in vitro* models used in the screening of COPD drugs.

2. Cellular models in COPD research

2.1 Primary human airway epithelial (HAE) cells

Primary HAE cells cultivated *in vitro* appear to be the most suitable model for research on the human respiratory epithelium functions in airway disorders. These patient-derived cells present a considerable benefit in investigating the pathophysiology of hereditary respiratory diseases, since they furnish respiratory cells with pre-existing genetic mutations, thereby minimizing the need for laboratory-based genetic alterations. This encompasses epigenetic modifications; studies reveal that primary airway cells derived from COPD patients have epigenetic DNA alterations and mimic epithelial responses to IL-13 [14]. Researchers have used co-culture models to investigate the effects of growing primary epithelial cells of the airway or cell lines in monolayer or air-liquid interface cultures. Nonetheless, cell lines are typically chosen as a substitute since natural airway epithelial cells require precise medium formulations. Furthermore, the supporting cell types that are incorporated into the co-culture models may be from sources or cell lines. Complementary cell types can include inflammatory and immunological cells or structural cells [15]. It has been noted that HAE cells can form areas of locally coordinated ciliary activity that demonstrate mucociliary transport over short distances when cultivated in the proper conditions near an air-liquid interface [16]. The ATP-binding cassette family of transporters is a comparatively underexplored factor in the biology of the respiratory mucosa. The expression of ABC transporters in HAE cells may enhance bronchial mucosal immunity by altering the pulmonary environment in reaction to surrounding stimuli, including smoking, allergenic substances, air pollution, and viruses [17]. However, the typical primary HAE culture possesses various drawbacks that have hindered its wider application in airway cell research. The primary and most important disadvantage of primary HAE cells is their poor capacity to effectively divide and multiply *in vitro* (**Figure 1**) [14].

2.2 Bronchial and alveolar cell lines

Epithelial cells in the alveoli constitute a critical barrier for maintaining pulmonary function. The human bronchial epithelium, serving as the primary defense of the respiratory system, is invariably subjected to cigarette smoke [18]. The BEAS-2B cell line is derived from healthy epithelial cells that have been immortalized by a hybrid virus consisting of adenovirus 12 and simian virus. The cells have been extensively utilized in studies on the anatomy and physiology of respiratory epithelial cells, such as cytokine regulation, glucocorticoid receptor modulation, phenotyping, and sensitivity to particles, smoke, and hyperoxia [19]. Studies show that when bronchial epithelial

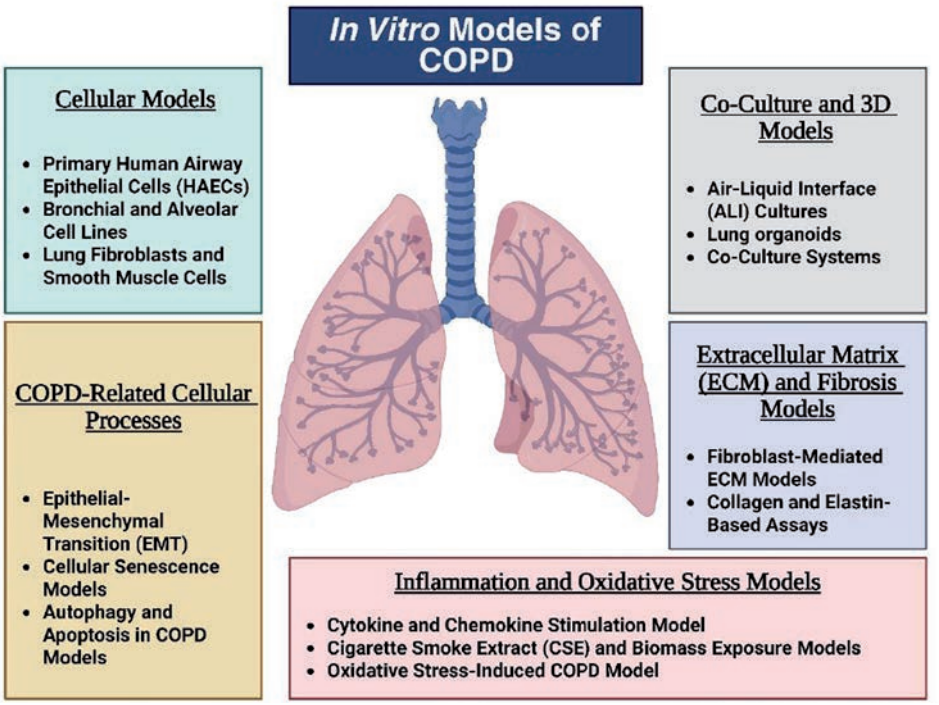


Figure 1.
Various in vitro *models are used to study chronic obstructive pulmonary disease (COPD). These include cellular models, co-culture and 3D systems, ECM and fibrosis models, and inflammation and oxidative stress models.*

cells and the BEAS-2B epithelial cell line supernatants were exposed to TNFα for 1 day, the production of IL-8 and RANTES increased in a concentration-dependent manner, while TGF-β levels were decreased. Higher synthesis of these two chemokines directly enhanced the mobility of smooth muscle cells in the airways, therefore facilitating the attraction of neutrophils and eosinophils in COPD patients [20]. Numerous *in vitro* investigations on lung epithelial cells have shown that diesel exhaust and its particles (DEP) provoke the secretion of several cytokines and chemokines involved in the inflammatory response related to both innate and adaptive immunity [21]. Furthermore, the most widely used cell line to simulate alveolar epithelial cells is the adenocarcinoma cell line A549. It is also most likely to have originated from these cells [15]. A549 cells subjected *in vitro* to oxidative stress and TNF exhibited elevated expression of TRAIL-R1, R2, and R3, alongside increased levels of p53. This suggests that oxidative stress and/or inflammatory cytokines may be responsible for the TRAIL system regulation seen in emphysematous lung, a defining feature of COPD. TRAIL, produced by activated inflammatory cells, may render alveolar cells more susceptible to its apoptotic effects due to the oxidative stress and inflammation characteristic of the emphysematous lung [22]. Another *in vitro* investigation, using the A549 adenocarcinoma and H1299 cell lines, as well as primary HAE cells, has demonstrated that cigarette smoke condensate can increase the synthesis of mRNA for several cytokines, such as IL-6 and CXCL8 (IL-8). They demonstrated that this was associated with a concurrent rise in NF-κB activity due to elevated oxidative stress [23]. A549 cells share numerous characteristics with alveolar type 2 cells; nevertheless, they are deficient in the essential capability of alveolar type II cells to establish a robust barrier (**Figure 1**) [15].

2.3 Lung fibroblasts and smooth muscle cells

Small airway illness results from ongoing airway remodeling, marked by chronic mucus hypersecretion and fibroblast activation, leading to increased synthesis of extracellular matrix (ECM) proteins and subsequent hardening of the airway wall [10]. Fibroblasts facilitate epithelial progenitor cell function by secreting paracrine substances such as Wnt ligands and fibroblast growth factors (FGFs) [24]. Researchers have utilized *in vitro* cell cultures, such as lung fibroblasts, to discover miRNAs linked to the formation of COPD [25]. Fibroblastic cells originate from localized epithelial cell conversion through cigarette-induced epithelial-mesenchymal transition (EMT), which is currently considered one of the processes involved in remodeling events linked to COPD etiology. Epithelial cells give up their distinctive polarity and cell-to-cell interactions during EMT in favor of a more mobile, mesenchymal phenotype. The majority of cell types undergo a metamorphosis from epithelium to fibroblast and then to myofibroblast [26]. Lung fibroblasts from humans are subjected to oxidative stress and cell death when exposed to cigarette smoke extract. COPD lung fibroblasts have impaired collagen gel contraction and repair functions. When compared to normal smokers and non-smokers of the same age, SAFs from COPD patients exhibited less proliferation and more expression of senescence markers. Furthermore, these cells release elevated levels of collagen types 1A1 and 3A1, as well as enhanced matrix metalloproteinases [27]. In addition to lung fibroblasts, bronchial smooth muscle cells in culture can modify several functions, including migration, proliferation, flexibility, and the synthesis of inflammatory mediators. The conversion of airway smooth muscle cells (ASMC) from a contractile to a synthetic or proliferative phenotype plays a role in the pathophysiology of asthma and COPD. These phenotypic alterations induce a dysfunction in ASMC activity [28]. Mucosal thickness in airway remodeling might exacerbate mucosal shortening, while muscle thickening may result in increased muscle shortening under elastic pressures. Additionally, when compared to a normal airway, the increased force-generating ability of the respiratory smooth muscle in COPD contributes to the increased airway constriction. This contributes to nonspecific bronchial hyperresponsiveness, a reliable indicator of the fast deterioration of forced expiratory volume in 1 second in individuals with COPD (**Figure 1**) [29].

3. Co-culture and 3D models

3.1 Air-liquid interface (ALI) cultures

A variety of epithelial cell types have been cultivated at ALI to replicate different sections of the respiratory tract. Cells from different parts of the respiratory system are cultivated at ALI and can recreate multiple aspects of the diseased condition [30, 31]. ALI-cultured HBECs serve as an *in vitro* model for human bronchi tissue. This model is employed to examine the biological impacts of aerosol compounds, including cigarette smoke (CS), as the respiratory epithelium acts as a barrier safeguarding the lungs from toxins. In biological research, cigarette smoke extract (CSE), which is made by either bubbling generated cigarette smoke through an aqueous solvent or eluting filter-trapped cigarette smoke particles, is frequently used to expose subjects to cigarette smoke. It has been demonstrated that the addition of CSE to the basolateral media of ALI-cultured HBECs alters the respiratory defense systems [32]. It

is typically created by two main procedures in most research settings. Initially, cells are extracted from pseudostratified respiratory tract segments through curettage or brushing. Second, the cells are cultured on a porous substrate coated with extracellular matrix, which comes in a variety of sizes and types [33]. Cells from several organs, including the nose, trachea, and tracheobronchial epithelial cells from humans and mice, can be cultured in an ALI environment. Additionally, the researcher can regulate the environment by giving cells cytokines, using ALI culture methods [34]. Investigations conducted using ALI airway cells have yielded substantial *in vitro* toxicity profiles of car emissions and environmental contaminants, which may facilitate *in vitro* and *in vivo* comparisons. Although certain research has employed ALI airway models derived from vulnerable populations, such as those with COPD, further study is necessary to evaluate the fidelity of these models in replicating toxicological reactions in high-risk groups (**Figure 1**) [35].

3.2 Lung organoids

Traditional 2D cell culture models are deficient in the complexity of multicellular layers and tissue architecture, hindering the precise replication of the COPD microenvironment and the capture of distinctive cellular relationships and pathology advancement in the human pulmonary system. Conversely, organoid models potentially more accurately replicate the cellular diversity and environment of the human lung by generating three-dimensional cellular architectures. They reproduce the interactions among the primary cell types linked to COPD, including epithelial cells, immunological cells, and fibroblasts, and encapsulate processes such as tissue remodeling, inflammatory reactions, and cellular migration [36]. When primary bronchial epithelial cells are combined with stromal cells in 3D culture conditions, the heterogeneous cell population swiftly condenses and self-organizes into epithelial and endothelial structures, resulting in the formation of airway organoids [37]. The cultural process encompasses two fundamental stages. Initially, before stem cell differentiation, essential signaling mechanisms that regulate developmental stages are meticulously regulated, either activated or suppressed, to establish appropriate regional identities. The culture subsequently advances through the integration of a 3D ECM that fosters a more intricate habitat [36]. Various stem cells and progenitor cells have been utilized to generate lung organoids, which are 3-D miniature models of the lung, owing to their capability to self-assemble and differentiate into many cell types. Lung organoids are often produced utilizing two categories of cells categorized by their ability to differentiate: multipotent adult stem cells (ASCs) and pluripotent stem cells (PSCs) [38]. The origin of the stem cells significantly affects the current cell types in lung organoids. Organoids generated from human PSCs exhibit a pronounced alveolar hallmark, predominantly including AT1 and AT2 cells [39]. Alveolar type I (AT1) and type II (AT2) cells sustain the alveolar epithelium in the lungs, which is vital for gas exchange and creates a robust barrier against the passive flow of fluid from the vascular compartments and interstitial into the alveolar cavity [40]. Lung organoids derived from adult tissue *via* bronchoalveolar lavage fluid or biopsies exhibit ciliated, basal, club, and goblet cells. Lung organoids exhibit a reduced presence of basal cells in comparison to HAE cells, while demonstrating an increased abundance of club and ciliated cells [39]. It serves as an *in vitro* model for the regeneration of the mucociliary epithelium from basal cells. Consequently, they can be utilized to evaluate regenerative mechanisms suggested by *in vivo*

investigations and to screen for pharmaceuticals, small compounds, and molecular pathways that might modulate cellular plasticity and lineage outcomes, along with essential epithelial cell functions (**Figure 1**) [41].

3.3 Co-culture systems

Co-culture models in the lung are extensively employed to examine modifications in alveolar-capillary barrier function, mechanisms of viral or particulate infection (epithelial-macrophage culture), epithelial-mesenchymal associations to investigate remodeling of airway operations, and the influence of smooth muscle mast cell interactions on the reconstruction of the airway [42]. The majority of co-culture models are engineered to replicate the spatial organization of cells within the epithelial-mesenchymal trophic unit (EMTU), which includes a reduced fibroblast sheath within an ECM produced by large stellate interwoven fibroblasts that are near a reticular beneath membrane and aid in lung epithelium adhesion. The lung-EMTU is triggered in pulmonary disorders to induce abnormal healing mechanisms [10]. Early studies of the conventional EMTU showed in a co-culture paradigm that fibroblasts' release of mediators affects the airway epithelium's proliferation as well as differentiation, while the airway epithelium in turn affects fibroblasts' capacity to proliferate. In 2006, Thompson and colleagues found that airway epithelial injury from scrape wounds increased the expression of α-smooth muscle actin, tenascin-C, and fibrillar collagen in lung fibroblasts encapsulated in collagen I gels [43]. Cellular interactions in the lung EMTU are assessed using conditioned media exposure experiments, epithelial-mesenchymal co-cultures, and 3D ECM co-cultures [44]. The development of co-cultures is a complex endeavor, as each cell type requires specific cellular media and supplements. Furthermore, the distribution of diverse cell types must reflect the *in vivo* conditions in both disease and normal states. Nonetheless, the formation of co-cultures remains viable due to the availability of numerous alternatives (**Figure 1**) [45].

4. Inflammation and oxidative stress models

4.1 Cytokine and chemokine stimulation model

Inflammatory cells, along with other types of structural cells like epithelial, endothelial, smooth muscle, and fibroblast cells, secrete tiny proteins called chemokines and cytokines, which regulate the movement and stimulation of inflammatory cells. TNF-α, interleukin (IL-1α, IL-1β, and IL-6), and interferon (IFN)-γ are cytokines associated with COPD [46]. IL-1α and IL-1β interact with the IL-1 receptor (IL-1R1) and are proinflammatory cytokines primarily produced by monocytes, macrophages, and fibroblasts. Mice lacking IL-1R1 demonstrate a reduced neutrophilic inflammatory response to cellular death, but not to bacterial infection, and display less tissue damage due to inflammation. Conversely, the acute monocyte response to cellular death, essential for tissue healing, is only marginally reduced, suggesting that the blockage of the IL-1 pathway will not affect the host's response to microbial infections. By binding to IL-1R and blocking the binding of IL-1α and IL-1β, the IL-1 receptor antagonist (IL-1RN or IL-1RA) neutralizes their activity and acts as an endogenous counterregulatory process [47]. Patients with COPD had higher concentrations of IL-6 in their plasma, exhaled breath, and mucus, especially

during flare-ups. Increased levels of C-reactive protein are associated with higher plasma concentrations of IL-6, and IL-6 is the primary mechanism that triggers the liver's release of C-reactive protein [48]. Conversely, TNF-α initiates the activation of NF-κB, a transcription factor that promotes the transcription of the IL-8 gene and increases the production of IL-8 from neutrophils and the airway epithelium. Bacteria and their byproducts, such as lipopolysaccharide, can cause IL-8 expression, most likely due to the initial generation of TNF-α. COPD patients have elevated levels of ICAM-1 in their serum due to an increase in TNF-α expression [49]. TNF-α and IL-1β are key cytokines that trigger inflammation during COPD exacerbations [50]. Due to increased monocyte recruitment from circulation caused by the monocyte-selective chemokines CCL2 and CXCL1, which are more abundant in COPD patients' sputum and bronchoalveolar lavage fluid, smokers and COPD patients have higher macrophage counts in their lungs [51]. Patients with COPD have elevated levels of certain CC-chemokines, including CCL-2 and CCL-3, which attract specific inflammatory cells into the airway, including neutrophils, macrophages, and CD8(+) T lymphocytes. This implies that every receptor contributes to the pathogenesis of disease (**Figure 1**) [50].

4.2 Cigarette smoke extract (CSE) and biomass exposure models

Cigarette smoking (CS), the main risk factor for COPD, affects the airway epithelial barrier and causes oxidative stress, which induces senescence and activates proinflammatory pathways. To investigate the cellular and molecular processes associated with elevated oxidative stress and to evaluate novel therapeutic strategies capable of reversing CSE-mediated tissue damage and cell damage, *in vitro* models of CSE-damaged airway epithelial cells represent a promising therapy approach for COPD patients. CS-induced oxidative stress results in LPO and DNA destruction, which subsequently produces neoantigens that elicit the formation of autoantibodies. Consequently, these events adversely affect various cellular activities, including autophagy, mitochondrial activity, and proliferation and survival [52]. The aryl hydrocarbon receptor pathway, inflammatory signaling, oxidative stress responses (Nrf2), and xenobiotic metabolism are all predicted to be elevated by smoking [53]. Significantly, CS exposure inhibits lung neutrophil mitochondrial activity, causing necrotic rather than apoptotic cell death. This is followed by the release of damage-associated molecular patterns (DAMPs), particularly HMGB1, which in turn causes healthy human bronchial epithelial cells to release more proinflammatory cytokines [54]. Research indicates that reactive oxygen species (ROS) in cigarette smoke causes hyaluronan fragmentation in bronchial epithelial cells *in vitro*, compromising barrier integrity by interacting with the epithelial surface receptor layilin and facilitating a RhoA/Rho kinase-mediated reduction in E-cadherin expression at both the genetic and protein levels. Another mechanism involves the CSE-induced reduction in transepithelial resistance and the delocalization of junctional scaffolding proteins ZO-1 and OCLN in airway epithelial cells *in vitro,* which was demonstrated to be dependent on EGFR [55]. Comparative analyses of responses obtained from cells derived from healthy donors vs. those from individuals with disease or heightened disease risk present an ethically permissible substitute for *in vivo* exposure investigations. Nonetheless, various factors constrain the efficacy of including *in vitro* investigations. *In vitro* investigations often require cells to be completely immersed in liquid growth media, frequently supplemented with serum. Incorporating biomass smoke into culture medium may result in the depletion of smoke activators and the formation of

potentially more hazardous byproducts due to interactions between the constituents of biomass smoke and the elements of the culture medium (**Figure 1**) [56].

4.3 Oxidative stress-induced COPD model

Oxidative stress seems to accelerate numerous pathogenetic pathways associated with COPD and its progression. This indicates that mitigating oxidative stress by antioxidants or by augmenting endogenous antioxidants could be a beneficial treatment strategy [57]. Numerous direct and indirect indicators of oxidative stress, such as aldehydes, thiobarbituric acid-reactive substances, hydrogen peroxide (H_2O_2), superoxide (O2-), 4-hydroxynonenal (4-HNE), and 3-nitrotyrosine (3-NT), are elevated in plasma, sputum, bronchoalveolar lavage, and lung tissues of COPD patients [58]. CS indirectly increases oxidative stress by affecting endogenous antioxidant systems, such as SOD, glutathione, and Nrf2. Oxidative stress activates proinflammatory pathways, alters DNA methylation and histones, and modifies non-coding RNA levels [52]. Additionally, oxidative stress influences mucous cell metaplasia and controls the activity of mucin genes, including MUC5AC. Apurinic/apyrimidinic sites, ubiquitous DNA damages from oxidized base repair, are greater in smokers without COPD, indicating active DNA repair, whereas COPD patients have impaired DNA repair mechanisms [59]. *In vitro* studies demonstrated that an increased level of Parkin in epithelial cells inhibited mitochondrial reactive oxygen species (ROS) generation, while CS extracts induced cell death. Research indicates that elevated Parkin levels accelerate mitochondrial scavenging and inhibit the progression of COPD [60]. The inflammatory chain reactions are susceptible to oxidative stress. They include redox-sensitive molecular targets as signaling entities, such as Ras/Rac, Jun-N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), the transcription factor NF-κB, and protein tyrosine phosphatases. The administration of the antioxidant GSH diminished the activation of the IkB kinase/NF-kB pathway in an *in vitro* investigation utilizing peripheral blood cells from COPD patients (**Figure 1**) [61].

5. Extracellular matrix (ECM) and fibrosis models

The extracellular matrix (ECM) in COPD undergoes considerable remodeling, affecting airway flexibility and regeneration. Changes in the ECM include inflammation, fibrosis, and epithelial malfunction which all aggravate lung injury and airflow limitation.

5.1 Fibroblast-mediated ECM models

In vitro models are utilized to investigate fibroblast-mediated extracellular matrix (ECM) in COPD. In these models, lung fibroblasts are cultured using ECM constituents like collagen and fibronectin. These models demonstrate the inability of COPD fibroblasts to contract 3D collagen gels, which are essential for maintaining the integrity of the ECM, and to repair damaged ECM components, including fibronectin. In COPD fibroblasts, an enhanced prostaglandin E2 (PGE2) synthesis and overexpression of EP2/EP4 reduce the repair mechanism by cyclic AMP signaling. There is a contradictory relationship between enhanced secretion of TGF-β1 and decreased sensitivity to its profibrotic effects [62]. Dysregulated TGF-β signaling causes aberrant ECM deposition that produces a rigid, fibrotic milieu with elevated

collagen I/III and laminin and reduced elastin and decorin [63]. Experimental evidence from a system that uses extracellular matrix (ECM) coated substrates shows that laminin and collagen I/III facilitate the proliferation, migration, and adherence of ASMC in COPD rat models *via* the PI3K/AKT pathway, resulting in the enlargement of the airway wall [64]. Decellularized bronchial scaffolds derived from patients with COPD also show that diseased extracellular matrix (ECM) alters epithelial differentiation and increases remodeling mediators such as hepatocyte growth factor (HGF) (**Figure 1**). These models show that the ECM contributes to the continuation of fibroblast dysfunction by highlighting bidirectional linkages and increasing ECM stiffness. Moreover, the balance of the ECM is further disturbed by mediators made by fibroblasts, like TGF-β1 (**Table 1**) [66, 71].

5.2 Collagen and elastin-based assays

The application of assays based on collagen and elastin may enhance comprehension of the pathophysiology, severity, and progression of COPD. Most of these assays are intended to assess fibroblast contractility and ECM degradation, both of which are significant factors in the fibrosis that is linked to COPD. The reconfiguration of pulmonary tissue characterizes COPD. As a result of this remodeling process, ECM fragments are released into the blood. These fragments can be identified as serological surrogate indicators of disease activity. These fragments, which comprise collagen

S.No.	Model type	Description	Application in COPD	References
1.	Fibroblast-mediated ECM models	Lung fibroblasts cultured with ECM components (e.g., collagen and fibronectin); altered TGF-β, PGE2 signaling	Evaluates ECM repair deficits, fibroblast dysfunction, and profibrotic signaling pathways	[65]
2.	ECM-coated substrate models	Laminin or collagen-coated substrates with ASMC	Assesses ASMC proliferation, migration, and PI3K/AKT pathway activation	[64]
3.	Decellularized bronchial scaffolds	Human bronchial ECM from COPD patients seeded with epithelial cells	Models epithelial remodeling and pro-remodeling mediator (e.g., HGF) expression	[66]
4.	Collagen gel contraction assays	3D collagen type I gel associated with lung fibroblasts	Measures fibroblast contractility and ECM remodeling capacity	[67]
5.	Elastin degradation assays	Elastin substrates treated with neutrophil elastase or fibroblasts	Mimics elastin breakdown relevant to emphysema development	[68]
6.	ECM-derived biomarker assays	Serum detection of ECM-derived fragments (C3M, C6M, Pro-C3, and EL-NE)	Provides non-invasive biomarkers for disease activity and progression	[69]
7.	Crosslinking assays	Quantification of ECM crosslinking markers (e.g., DHLNL)	Evaluates matrix stiffness and response to anti-fibrotic interventions	[70]

Table 1.
Various types of models with their utilization in COPD.

types I, III, IV, VI, biglycan, elastin, and others, can be assessed by assays to help identify patient at risk for the progression and mortality of their condition [72, 73]. There is a connection between the function of the lungs and the amount of neutrophil elastase-derived fragments of elastin (EL-NE), type VI collagen (C6M), and collagen type III (C3M) in the blood. A decrease in pro-C3 and C6 levels is associated with heightened severity of airflow restriction, hyperinflammation, air entrapment, and emphysema, whereas C3M and C6M are connected to dyspnoea [72]. Moreover, studies indicate that COPD patients exhibiting increased levels of collagen remodeling indicators are at a heightened risk of mortality. This indicates that assessing tissue turnover in the parenchyma and small airways may enhance COPD prognosis [73]. Fibrotic disease, such as idiopathic pulmonary fibrosis (IPF), can be caused by changes in the post-translational crosslinking of the ECM. An innovative method for tracking crosslinking dynamics has been developed, which reduces the need for specialized equipment and manual work. This method shows that fibrotic murine models and human pulmonary fibrosis (IPF) lungs have higher levels of dihydroxylysinorleucine (DHLNL), suggesting that anti-fibrotic drugs might help with these symptoms (**Figure 1**). To evaluate the effectiveness of pharmacological drugs, these tests are vital in the field of COPD research and therapy development (**Table 1**) [74].

6. Mimicking COPD-related cellular processes

6.1 Epithelial-mesenchymal transition (EMT)

EMT is a cellular mechanism in which epithelial cells lose their intracellular adhesion and polarity and instead take on mesenchymal traits, such as enhanced migratory and invasive capacities. EMT is associated with small fibrosis, the fundamental cause of physiological airway dysfunction in COPD patients. EMT in COPD comes in different forms: type 2 EMT is associated with fibrosis, while type 3 EMT is associated with angiogenesis and the emergence of cancer. Models relevant to COPD (TGF-β) play a crucial role as an inducer of ECM, mimicking the airway remodeling found in patients. TGF-β facilitates EMT through both Smad-dependent and non-Smad-dependent pathways, resulting in downregulation of epithelial markers, including E-cadherin, and overexpression of mesenchymal markers such as vimentin. These changes result in the formation of fibroblasts, which encourage the deposition of ECM and remodeling of airways [75–77]. Studies demonstrate that EMT might occur tiny and big airways of smokers or patients who have COPD. EMT indicators such as alpha smooth muscle actin are found beneath the reticular basement membrane in tiny airways, indicating structural changes associated with fibrosis. Moreover, the fragmentation of Rbm and hypercellularity are characteristic attributes of EMT in these tissues [76, 78]. Conversely, substantial airway epithelial-mesenchymal transition (EMT) is typically achieved through angiogenesis (type-3 EMT), potentially elucidating the elevated lung cancer risk in individuals with COPD [75, 79]. Experimental models utilizing TGF-β have successfully mimicked these pathogenic characteristics, thus demonstrating its essential role in promoting airway remodeling associated with EMT (**Figure 1**) [80].

6.2 Cellular senescence models

Cellular senescence is a vital biological phenomenon marked by an irreversible cessation in growth and release of inflammatory mediators, profoundly influencing

the advancement of COPD. Senescent cells target lung tissues in COPD, resulting in senescence-associated secretory phenotype (SASP), which causes dysregulation of tissue repair and persistent inflammation. The presence of these inflammatory environments causes damage to the lungs and accelerates the progression of other diseases. In most cases, oxidative stress or telomere reduction are the mechanisms that are used to generate *in vitro* senescence in models of cellular senescence in COPD. For instance, it has been shown that lung fibroblasts undergo cellular senescence as a result of exposure to oxidative compounds such as Paraquat. The aging phenotype in these cells is suggested by increased marker expression like p16INK4a and senescence-associated β-galactosidase [81, 82]. Moreover, telomere attrition resulting from successive cell division or oxidative stress may trigger replicative senescence, hence intensifying the accumulation of dysfunctional less in the COPD patients [83]. Research shows that these aged cells not only multiply less, but also produce a plethora of proinflammatory cytokines. These factors contribute to the pathophysiology of COPD by prolonging the inflammatory cycle and facilitating tissue remodeling [84, 85]. Therapeutic methods that target senescent cells or their secretory patterns to alleviate symptoms of disease and delay progression have great promise, thanks to the identification of cellular senescence in COPD models (**Figure 1**). Therapeutic methods that target senescent cells or their secretory patterns to alleviate symptoms of disease and delay progression have great promise, thanks to the identification of cellular senescence in COPD models [82, 83].

6.3 Autophagy and apoptosis in COPD models

Autophagy and apoptosis are interconnected mechanisms that promote cell death in COPD, with experimental models employing specific stresses to elucidate their roles. Autophagy, a lysosomal breakdown process, is examined in COPD models by dietary deprivation or pharmaceutical drugs like rapamycin, which inhibits mTOR to enhance autophagic flux. In mouse models, the administration of rapamycin enhances LC3-II/LC3-I ratios (a marker of autophagosome formation) while reducing p62 levels, signifying heightened autophagy activation. This intervention paradoxically induces apoptosis in COPD in mice, suggesting that dysregulated autophagy leads to cell death. Moreover, starving models can simulate nutrient-deficient environments, hence triggering ULK1-mediated autophagic initiation through the inhibition of mTOR-dependent pathways [86, 87]. These methods illustrate that, whereas autophagy initially protects against oxidative stress by removing damaged mitochondria, its decline in COPD is ineffective in clearing ROS, leading to dysfunction of mitochondria and apoptotic signaling [88]. In models of COPD, apoptosis is triggered by oxidative stress or caspase activators. Cigarette smoke extract (CSE) initiates the extrinsic apoptosis pathway by generating death-inducing signaling complexes (DISC), subsequently activating caspase-8 and caspase-3 in lung epithelial cells. Oxidative stress models subject mice to cigarette smoke, elevating ROS levels, diminishing the activity of the anti-apoptotic protein Bcl-2, and promoting caspase-3 cleavage. Antioxidants like vitamin E decrease these effects, thereby confirming the role of ROS in the apoptotic signal. Pharmacological and genetic inhibition of DNMT1, a protein that links oxidative stress to hypermethylation of the Bcl-2 promoter, lowers mortality and enhances pulmonary function in animal models of COPD. More specifically, autophagy and mortality often occur simultaneously: At the same time that CSE upregulates LC3B lipidation and caspase activation, siRNA reduction of autophagy regulators (such as Beclin-1 and LC3B) decreases DISC formation and death (**Figure 1**) [89, 90].

7. Drug screening and therapeutic testing in COPD models

7.1 High-throughput screening (HTS) platforms

HTS systems have become crucial tools in drug discovery, especially for COPD. These systems provide the fast evaluation of many drugs against *in vitro* models that precisely mimic the pathophysiology of COPD. Recent developments in HTS technologies, including bronchus-on-a-chip systems and bronchosphere models, have greatly improved the capacity to replicate airway inflammation and mucus hyperproduction, fundamental characteristics of COPD. For example, the bronchus-on-a-chip (BoC) system permits epithelial cells cultured in a tubular shape that duplicates human bronchial epithelium, therefore creating a suitable environment for aerosol exposure and enabling high-throughput experiments [91]. In addition, broncho sphere models were successfully used to investigate disease-related pathways and potential therapeutic compounds using human bronchial epithelial cells. These models demonstrate phenotype alterations induced by exposure to CSE, including reduced spheroid size and enhanced production of mucins, such as MUS5AC, indicative of COPD. A recent research utilizing a 301 chemical library identified many targets that either restored spheroid size or diminished mucin formation, thereby demonstrating the potential of HTS screening to discover an appropriate therapeutic drug [92]. By incorporating HTS platforms into COPD studies, researchers can improve drug development and make their findings more applicable to real-world scenarios. Researchers can improve their ability to forecast medication efficacy and safety profiles by using models that faithfully represent human disease states (**Figure 2**) [93, 94].

7.2 Testing of anti-inflammatory and antioxidant compounds

The assessment of anti-inflammatory and antioxidant agents in drug screening and therapy for COPD has progressively depended on sophisticated *in vitro* models.

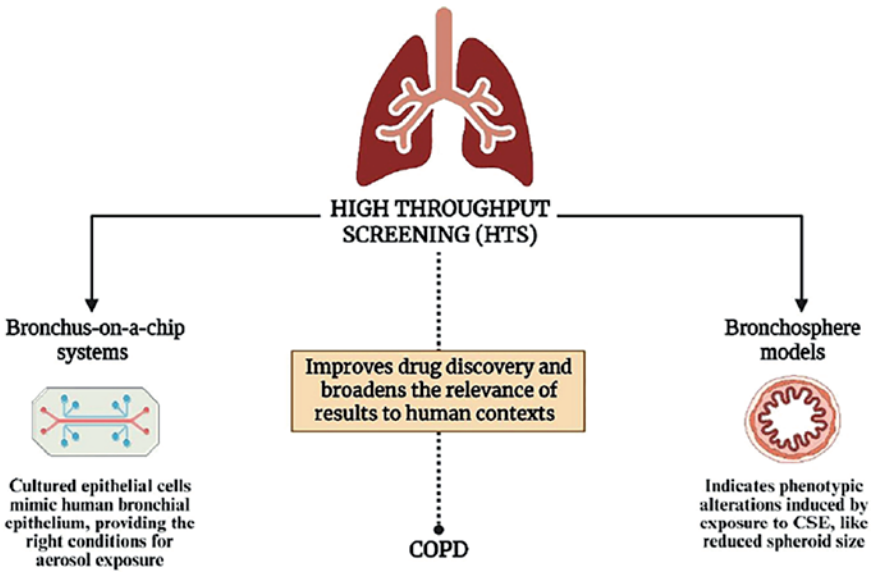


Figure 2.
HTS platforms like bronchus-on-a-chip and bronchosphere models facilitate COPD research and therapeutic screening.

In vitro studies of disease processes and treatment efficacy can be conducted in a controlled setting using human bronchial epithelial cells (HBE) and an organ-on-a-chip (OOC) model. For instance, it has been shown that exposure to the prevalent environmental pollutant PM2.5 can effectively develop COPD in HBE cells. This method demonstrated the medicinal promise of RTA-408, an artificial oleanane triterpene that inhibits oxidative stress and proinflammatory mediators, including NF-κB and IFN-γ, by Nrf3/hO-1 activation. Studies conducted both *in vitro* and *in vivo* have shown that RTA-408 can restore damaged cells and slow the advancement of illness [95, 96]. The thiol antioxidant N-acetyl-cysteine (NAC) restores the respiratory chain and protects mitochondria from oxidative damage. Its capacity to diminish inflammation relies on inhibiting the production of specific cytokines, including IL-6 and IL-8, which are crucial for neutrophil activation in the airways and are regulated by NF-κB. Research has indicated that the use of NAC in nutraceutical formulations can lead to better clinical outcomes. These outcomes include exercise tolerance, lower COPD Assessment Test scores, and lower levels of IL-8 in patient nasal lavages [97–99]. Furthermore, *in vitro* evaluations of p38 inhibitors like SB203580 have been conducted using lung cells and patient samples. By controlling levels of cytokines like TNF-α and IL-10, these inhibitors reduce systemic inflammation in COPD caused by lipopolysaccharide [100]. Advanced *in vitro* platforms, including induced pluripotent stem cell (iPCSs) based models and OOC systems, substantially enhance drug discovery by more precisely replicating human lung function. These models provide insight into inflammatory patterns at the tissue level and allow for pharmacological assessment of new drugs [101, 102]. *Ex vivo* methods, such as isolated human bronchial tissues, complement *in vitro* investigations by allowing exact evaluations of drug-drug interaction and inflammatory profile relevant to human physiology. Antioxidant formulations evaluated on primary bronchial epithelial cells have demonstrated potential in reestablishing cellular homeostasis impaired by cigarette smoke extract (CSE), nevertheless, additional research is required to confirm their impact on innate immune responses [96]. The advantages of using *in vitro* models include fewer ethical concerns than with animal research, quicker results, and reduced costs. Nonetheless, they possess limitations, including the inability to fully replicate systemic interaction found in *vivo*. Notwithstanding these difficulties, the integration of *in vitro* data with *in vivo* investigations might improve the knowledge of the therapeutic possibilities of a molecule [103, 104].

7.3 Gene editing and CRISPR-Cas9 applications

Gene editing technologies, particularly CRISPR-Cas9, have transformed the investigation of COPD by utilizing sophisticated *in vitro* models that replicate disease pathways and evaluate therapeutic approaches. A crucial method entails utilizing iPCSs obtained from patients, which are transformed into epithelial cells of the lung, especially type 2 alveolar epithelial cells (iAT2), to investigate genetic variations related to COPD. For instance, nine COPD-linked genes found by genome-wide association studies (GWAS) in iPSC-derived iAT2 cells have been knocked down using CRISPR interference (CRISPRi), therefore exposing changes in transcriptional programs vital to alveolar repair and epithelial-mesenchymal transition [105]. These models permit researchers to understand how dysregulation of genes such as HHIP and FAM13A causes reduced lung regeneration and chronic inflammation, the main features of COPD [105, 106]. Another new *in vitro* approach entails *ex vivo* gene editing of airway stem cells isolated from individual patients, utilizing CRISPR-Cas9 to

rectify mutations in cultivated bronchial epithelial cells before transplantation. This approach has been employed to focus on genes associated with mucus hypersecretion and oxidative stress responses, including MUC5AC and NFE2L2, offering insights into tailored therapy strategies [107]. Moreover, CRISPR-modified cell lines facilitate the modeling of the fibrinolytic system and epithelial-mesenchymal transition pathways, which are disrupted in the pathogenesis of COPD. For example, modifying TGF β signaling components in bronchial epithelial cells clarifies their function in causing fibrosis and airway remodeling [107, 108]. Recent developments have also made use of organoids grown from patients to investigate CRISPR-corrected mutation in a 3D microenvironment. These organoids replicate characteristics such as ciliary failure and chronic inflammation, facilitating HTS of gene editing effectiveness and drug candidates [106, 109]. Additionally, lipid nanoparticles (LNPs) and CRISPR-Cas-9 have been used to transport editing components transiently into primary lung cells *in vitro*, reducing off-target effects and allowing for precise gene alteration such as SERPINA1 (linked to alpha-1 antitrypsin deficiency) [110]. Such models provide a platform to validate therapeutic targets like IL-12 or STAT6 in Th2-driven inflammation and CRISPR's ability to alter disease phenotypes at the cellular level. These *in vitro* systems progress our comprehension of COPD pathophysiology and promote the development of gene treatments provided to certain molecular subtypes by including multi-omics data [106, 107]. Nevertheless, there are still lots of obstacles to overcome before these discoveries can be applied in clinical settings. The effectiveness and specificity of the delivery mechanisms for CRISPR-Cas9 are necessary for the successful implementation of these techniques in human therapeutics applications. In the past, viral vectors have been utilized for gene delivery. However, there are emerging non-viral techniques, such as lipid nanoparticles, that show promise in terms of improving the safety profile and lowering off-target effects. As research advances, enhancing these delivery systems will be crucial for unlocking the complete potential of CRISPR-based therapeutics in the treatment of COPD and other respiratory ailments [106, 111].

8. Challenges and future perspectives

The *in vitro* models that are currently being used to stimulate COPD have several limitations that compromise their ability to accurately represent the complexity of the disease that affects humans. Although various models, including immortalized cell lines and primary cells, allow for controlled research, they sometimes fail in stimulating the intricate microenvironment of the human lung. Although replicable and easy to maintain, immortalized cell lines might not accurately replicate the physiological features of lung cells, which could result in possible differences in medication response and disease progression investigations [112]. Although they are limited by their availability and the difficulties in preserving their viability over a long culture, primary cells obtained from patients give more relevant biological insights [113]. In addition, removing the cells from their natural ECM during the culture procedure may change the experimental outcomes, which lessens the applicability for translation. Additionally, the complex interactions between different types of cells involved in the pathogenesis of COPD are sometimes not repeatable by existing models, which is essential for comprehending disease causes and creating efficient treatments [112, 114]. The integration of *in vitro* models with *in silico* and *in vivo* methodologies is increasingly favored to augment the prediction capacity of COPD research. *In silico*

models are a great way to supplement experimental data from *in vitro* investigations. They may simulate complex biological processes and predict medication interactions and effectiveness using computer approaches [114]. Nevertheless, challenges persist in ensuring that these models accurately reflect human disease characteristics and that findings from animal research are effectively translatable to clinical settings [100, 113]. Modern methods like bioprinting and OOC are revolutionizing COPD studies by providing a sophisticated platform that faithfully imitates the functioning of real organs. OOC employs microfluidic technology to construct microscopic models of human lungs that stimulate physiological activities and responses to stimuli, facilitating HTS screening of possible therapeutics [114]. Bioprinting enhances this field by enabling the fabrication of complex 3D lung tissues composed of several cell types arranged to replicate natural architecture [100]. The future of COPD drug discovery is expected to enhance a more personalized approach, utilizing advancements and innovative therapeutic modalities. It is becoming possible to create targeted treatments that target particular mechanisms implicated in the progression of COPD as our knowledge of the molecular etiology of the disease increases. Incorporating advanced modeling approaches, such as OOC and bioprinting, into drug development pipelines is essential for enhancing screening methodologies and identifying novel compounds with improved success rates in clinical trials. Furthermore, continuous investigation into biomarkers will be essential for predicting treatment responses and providing drugs tailored to the specific profiles of individual patients. To enhance patient outcomes, researchers are using creative ways to overcome the limits of present COPD therapy options. The goal is to produce more effective therapeutic approaches.

9. Conclusion

In vitro models are crucial instruments for enhancing the comprehension of COPD, providing significant insights into disease mechanisms and facilitating the creation of novel therapeutics. Traditional immortalized cell lines offer convenience and reproducibility, but they frequently do not replicate the physiological intricacies of human lung tissue, which may restrict their applicability in pharmacological testing and disease modeling. Conversely, primary human airway epithelial cells more accurately represent disease phenotypes and responses since they maintain patient-specific genetic and epigenetic traits. The advancement of 3D culture systems, including lung organoids and ALI models, has significantly improved COPD research by accurately mimicking the anatomy and physiology of HBE. The study of important cell-to-cell and cell-to-matrix interactions in inflammation, oxidative stress, and tissue remodeling can be made possible by these state-of-the-art models. Incorporating immune and stromal cell into co-culture systems increases their biological significance, while OOC platforms and bioprinting technologies replicate dynamic physiological settings, facilitating HTS drug screening and tailored therapeutic approaches. Notwithstanding these achievements, numerous difficulties persist. *In vitro* systems frequently fail to replicate the comprehensive complexity of COPD, encompassing vascular involvement, systemic immunological responses, and interactions with the extracellular matrix. Furthermore, extracting cells from their natural environment may modify their behavior, thereby diminishing the translational significance of the results. *In vitro* drug concentrations may not adequately represent *in vivo* pharmacokinetics, perhaps leading to an overestimation of therapeutic benefits. Innovative

technologies like CRISPR-Cas9 gene editing and lipid nanoparticle delivery systems present novel opportunities to explore and potentially rectify mutations that contribute to diseases. Simultaneously, multi-omics methodologies utilizing patient-derived cells and organoids are facilitating the categorization of COPD into molecular subgroups, thereby advancing precision therapy. The integration of biomarkers to assess therapeutic response will be essential for clinical translation and the efficacy of tailored interventions.

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Chapter 4

Cerebral Oxygenation during a Walk Test in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) frequently experience exercise-induced hypoxemia (EIH). However, most studies that evaluated cerebral oxygenation during exercise using near-infrared spectroscopy (NIRS) did not consider the influence of facial blood flow. We aimed to investigate the frontal cerebral cortex oxygenation (COX) state during the 6-min walk test (6MWT) in patients with COPD who experienced EIH (COPD-EIH) using portable NIRS and hemodynamic modality separation (HMS) to eliminate the influence of facial blood flow. Six male outpatients with COPD (COPD group) and eight healthy men (healthy group) were enrolled in this study. Oximetry-measured blood oxygen saturation (SpO_2), pulse rate, and COX were continuously measured during the 6MWT. COX was measured using multichannel NIRS and HMS. Changes (Δ) in oxygenated hemoglobin (oxy-Hb), deoxygenated (deoxy)-Hb, and total Hb levels were analyzed. The COPD group showed significantly decreased SpO_2 (from 94.0 ± 1.2% to 85.7 ± 2.2%), significantly increased Δdeoxy-Hb, and significantly decreased Δoxy-Hb and Δtotal Hb during the 6MWT. In contrast, no significant changes were observed in each ΔHb in the healthy group. In conclusion, patients with COPD-EIH experience desaturation and hypoperfusion of the frontal lobe during the 6MWT. Thus, the duration and extent of hypoxia in the patients' daily lives should be measured and considered when determining the indication for oxygen administration.

Keywords: cerebral oxygenation, near-infrared spectroscopy, hemodynamic modality separation, chronic obstructive pulmonary disease, six-min walk test

1. Introduction

Patients with chronic obstructive pulmonary disease (COPD) frequently experience exercise-induced hypoxemia (EIH), which can cause exercise intolerance. A 6-min walk test (6MWT) is more sensitive than a cycle cardiopulmonary exercise test for identifying EIH in patients with COPD [1, 2]. However, the 6MWT induces hypoxemia in 40–70% of resting non-hypoxemic patients with COPD [1–4]. Thus, hypoxemia occurs frequently in the daily life of patients with COPD [5–8] because of the many activities related to

walking (walking, carrying loads, and ascending and descending stairs). Furthermore, hypoxemia at rest is a risk factor for cognitive impairment in patients with COPD [9].

The influence of EIH on the brain can be evaluated by cerebral oxygenation state (COX), which estimates the balance between oxygen supply and oxygen consumption. Near-infrared spectroscopy (NIRS) is a non-invasive technique for evaluating COX (10). This optical technique uses the absorption of near-infrared light of 700–900 nm and allows for qualitative and non-invasive *in vivo* assessment of changes in oxygenated (oxy-) and deoxygenated (deoxy-) hemoglobin (Hb) levels in small arterioles, venules, and capillaries, wherein the total Hb (oxy-Hb + deoxy-Hb) level is indicative of the blood volume in the observed region [10]. NIRS can be used to measure the outer cerebral cortex and superficial muscles [10]. Several studies investigating prefrontal COX during cycle ergometer using NIRS in patients with COPD [11, 12] showed that oxy-Hb and total Hb increased during constant workload cycle exercise [13–17].

However, NIRS has several disadvantages. First, many models are not portable, and thus, measurements cannot be taken during free walking or running. To the best of our knowledge, no study has measured COX during walking in patients with COPD despite the recent development of portable NIRS devices [18]. Second, NIRS signals originating from the cerebral tissues are difficult to separate from those originating from extracerebral tissues, such as the scalp, skull, and frontal sinus [19, 20]. To assess COX during exercise, signals from cutaneous blood flow in the forehead should be removed. However, most previous studies on COX during exercise did not consider the influence of facial blood flow. The multi-distance probe arrangement method (MPAM) [19, 20] has been used to eliminate the influence of facial blood flow. MPAM has the disadvantage of requiring a dedicated probe, which requires specialized equipment. Hemodynamic modality separation (HMS) [21–23] is a recently developed method that can be performed using commercially available equipment.

Therefore, this study aimed to investigate COX during the 6MWT in patients with COPD who experienced EIH (COPD-EIH), using portable NIRS. COX was calculated using HMS to eliminate the influence of facial blood flow.

2. Materials and methods

2.1 Study design and participants

This pilot study enrolled six male patients with COPD (COPD group) and eight healthy male controls (healthy group). All patients with COPD were outpatients attending Tokai University Hospital and had clinically stable disease for at least 3 months before the study. Patients experienced hypoxemia (oximetry-measured blood oxygen saturation (SpO_2) ≤88%) during the 6MWT, but SpO_2 at rest was ≥93%. Patients who had dementia, a history of cerebrovascular disease, or heart failure (HF), or who participated in any physical training program were excluded. Healthy participants were staff members at our university aged >60 years who did not have cardiopulmonary or cerebrovascular disease and were recruited using posters.

2.2 Study protocol

The participants were interviewed about their present and past medical history. Height, weight, blood pressure (BP), and pulmonary function were measured before

the 6MWT. Vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV_1) were measured using spirometry (SP-370COPD, Fukuda Denshi Co., Tokyo, Japan), and VC (%predicted), FEV_1/FVC, and FEV_1(%predicted) were calculated. Arterial blood gas analysis (ABG) was performed in the COPD group. Thereafter, participants performed the 6MWT. Continuous measurements of SpO_2, pulse rate (PR), and forehead NIRS were performed in an upright position from 1 min prior to the 6MWT (i.e., during rest) to the end of the 6MWT. The walking distance (6MWD) was measured, and symptom scores for breathlessness and perceived exertion were recorded using the Borg scale [24].

2.3 Experimental procedures

2.3.1 6MWT

The 6MWT was performed in a 50-m corridor according to previous guidelines [24], without supplemental oxygen, and supervised by a physician and a nurse. The nurse walked diagonally behind the participants using a portable NIRS device. The participants were allowed to stop if they experienced severe dyspnea and resumed walking when their symptoms subsided.

2.3.2 Pulse oximetry

SpO_2 and PR were continuously recorded using a pulse oximeter (PULSOX®-Me300, KONICA MINOLTA Inc., Tokyo, Japan), which was attached to the right index finger. To attenuate the motion artifact, the participants were asked to put their right hand on the center of their chest. EIH was defined as a 4% drop in SpO_2 from baseline, reaching a minimum of ≤88% [3, 25]. SpO_2 and PR were evaluated at rest and every minute from 1 to 6 min (SpO_2-n, PR-n; n = 1–6). SpO_2 and PR at rest (rest-SpO_2 and rest-PR, respectively) were the average values during the 30 s before the 6MWT. The difference in SpO_2 or PR between rest and each minute was calculated (ΔSpO_2-n or ΔPR-n). The lowest SpO_2 (SpO_2-low) and the highest PR (PR-high) values during the 6MWT were recorded.

2.3.3 NIRS measurements

2.3.3.1 Near-infrared spectrometry

A multichannel near-infrared spectrometer (Spectratec OEG16-SpO_2, Spectratec Inc., Tokyo, Japan) was used. The device used two near-infrared wavelengths (i.e., 770 nm and 840 nm) and took a measurement every 0.082 s. It could be powered by batteries and was portable. A 16-channel band-type optode holder (sensor band), consisting of two rows and six columns of alternating light transmitters and receivers at a distance of 3 cm (**Figure 1**), was placed on the forehead of each participant. The line through the lowest optodes was along the Fp7-Fp1-Fp2-Fp8 line of the international 10–20 system of electroencephalography. To calculate the amount of oxy-Hb and deoxy-Hb from the absorption rate of two different wavelengths, we used the modified Beer–Lambert method because of the high tissue scattering factor [10, 18]. Considering that this device used continuous light and could not detect the exact path length of the light, the result was denoted as the amount of Hb × pathlength (mM × mm). Thus, the obtained result was a relative value and not an absolute value.

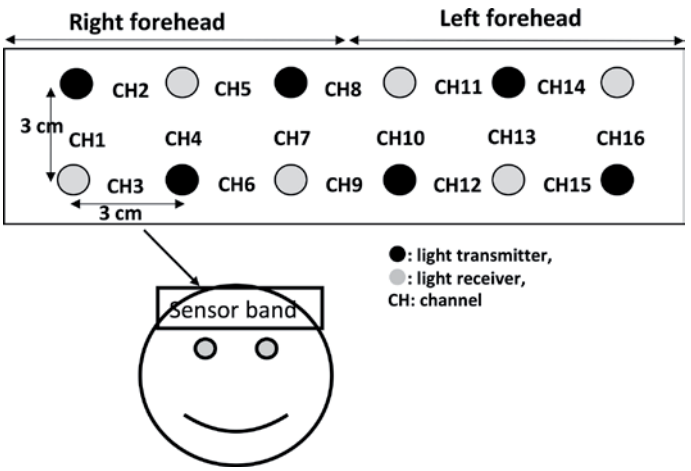


Figure 1.
Measurement sites and probes for the oxygenation status of the brain. The sensor band was placed on a participant's forehead.

2.3.3.2 HMS

We used the HMS method to separate the conventional NIRS signal into functional cerebral signals and other physiological signals. The details and evaluation of the HMS have been described in previous studies [21–23]. The functional cerebral signals obtained with HMS are highly consistent with those estimated with MPAM in situations such as body tilt, finger tapping tasks, and breath holding [22, 23]. HMS was built into the analysis software of the spectrometer that we used and could also be analyzed using previously measured data.

2.3.3.3 Data analysis

The oxygenation state was evaluated by changes (Δ) in oxy-, deoxy-, and total Hb in the functional cerebral signals. In each channel, for each minute during the 6MWT, the mean value of each ΔHb during the previous 30 s was calculated. Changes over time due to walking were examined by setting the value at the onset to zero and subtracting the value at the onset from the value of each ΔHb for each minute (ΔHb-n, n = 0–6). The oxygenation statuses of the frontal lobes were assessed by the mean of each ΔHb value of channels 1–16, excluding channels 7–10 because they contained only a portion of brain tissue.

2.4 Statistical analysis

Data are expressed as mean ± standard deviation (SD). Differences between the COPD and healthy groups were analyzed using an unpaired t-test. We performed a two-way repeated measures analysis of variance (ANOVA) with time course changes in SpO_2, PR, and each ΔHb as intragroup differences and two groups as intergroup differences, followed by Holm's post hoc test. All statistical analyses were performed using HAD version 17.102 (Hiroshi Shimizu, Kwansei Gakuin University, Kobe, Japan) [26]. A p value of <0.05 was considered statistically significant.

3. Results

3.1 Participant characteristics

The COPD group was older than the healthy group, but the difference in age was not significant (71.8 ± 2.9 years vs. 68.1 ± 4.0 years). Height, weight, body mass index, and BP were also not significantly different between the two groups. Meanwhile, the pulmonary function indicators of FEV_1, FEV_1/FVC, and FEV_1 (%predicted) were significantly lower in the COPD group than in the healthy group. All patients in the COPD group had arterial oxygen tension (PaO_2) >60 mmHg and arterial carbon dioxide tension ($PaCO_2$) <45 mmHg. The patient characteristics are shown in **Table 1**.

3.2 6MWT

All participants performed the 6MWT without interruption or discontinuation. The 6MWD was significantly shorter in the COPD group than in the healthy group ($p < 0.01$). Rest-SpO_2 and SpO_2-low were significantly lower in the COPD group than in the healthy group ($p < 0.01$), whereas rest-PR was significantly higher in the COPD group ($p < 0.05$). However, PR-high did not differ between the two groups. The dyspnea score was significantly higher in the COPD group than in the healthy group ($p < 0.05$); however, fatigue scores did not differ between the two groups. The 6MWT data are presented in **Table 2**.

		Healthy (n = 8)			COPD (n = 6)			p	
Age	**years**	**68.1**	**±**	**4.0**	**71.8**	**±**	**2.9**	**0.079**	
Height	cm	168.4	±	5.3	168.3	±	6.2	0.989	
Weight	kg	63.5	±	5.3	65.6	±	10.0	0.622	
BMI	kg/m^2	22.4	±	1.9	23.2	±	3.9	0.590	
Syst. BP	mmHg	128.8	±	20.7	137.5	±	10.2	0.363	
Diast. BP	mmHg	76.0	±	9.5	80.8	±	8.8	0.351	
VC	L	3.88	±	0.65	3.53	±	0.94	0.461	
VC (%predicted)	%	100.6	±	10.5	95.8	±	24.0	0.646	
FEV_1	L	2.91	±	0.52	1.30	±	0.53	0.000	*
FEV_1/FVC	%	80.6	±	4.9	46.5	±	11.4	0.000	*
FEV_1 (%predicted)	%	94.1	±	11.5	45.4	±	19.3	0.001	*
pH					7.399	±	0.013		
$PaCO_2$	mmHg				40.1	±	3.8		
PaO_2	mmHg				74.8	±	4.9		

*BMI: body mass index; Syst. BP: systolic blood pressure; Diast. BP: diastolic blood pressure; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $PaCO_2$: arterial carbon dioxide tension; PaO_2: arterial oxygen tension. Values are presented as mean ± SD. *: $p < 0.01$ between the healthy group and the COPD group.*

Table 1.
Profiles of participants.

		Healthy (n = 8)			COPD (n = 6)			p	
6MWD	**m**	**585.9**	**±**	**47.7**	**495.7**	**±**	**59.7**	**0.008**	**
Rest-SpO_2	%	97.8	±	1.3	94.0	±	1.2	0.000	**
SpO_2-low	%	95.5	±	1.5	85.7	±	2.2	0.000	**
Rest-PR	bpm	74.1	±	9.2	88.0	±	7.6	0.011	*
PR-high	bpm	128.3	±	14.1	126.3	±	12.8	0.798	
Dyspnea score		2.3	±	2.7	5.5	±	2.1	0.031	*
Fatigue score		2.1	±	2.4	2.5	±	2.6	0.782	

*6MWD: 6-min walk test distance, SpO_2: oximetry-measured blood oxygen saturation, Rest-SpO_2: SpO_2 at rest, SpO_2-low: the lowest value of SpO_2 during the 6-min walk test; Rest-PR: pulse rate at rest; PR-high: the highest value of pulse rate during the 6-min walk test. Values are presented as mean ± standard deviation. *: p < 0.05, **: p < 0.01 between the healthy and the COPD group.*

Table 2.
Data of the 6-min walk test.

The changes over time in SpO_2 and PR are shown in **Figure 2**. The ANOVA revealed a significant between-group difference in SpO_2, lapsed time, and interaction effects. The simple main effects showed a significant difference in the COPD group ($F(6, 72) = 32.627$, $p < 0.01$), but not in the healthy group ($F(6, 72) = 1.070$, $p = 0.365$). SpO_2 during the 6MWT significantly decreased from 2 min to 6 min compared with that at rest ($p < 0.01$) and at the first minute ($p < 0.01$) in the COPD group (**Figure 2**). The ANOVA revealed a significant difference in PR in the lapsed time. However, there were no significant differences in the group factor and interaction effects. Meanwhile, the simple main effects showed a significant difference between the COPD group ($F(6, 72) = 17.497$, $p < 0.01$) and the healthy group ($F(6, 72) = 31.954$, $p < 0.01$). PR during the 6MWT was significantly higher from 1 min to 6 min than that at rest in both the COPD group ($p < 0.01$) and the healthy group ($p < 0.01$) (**Figure 2**).

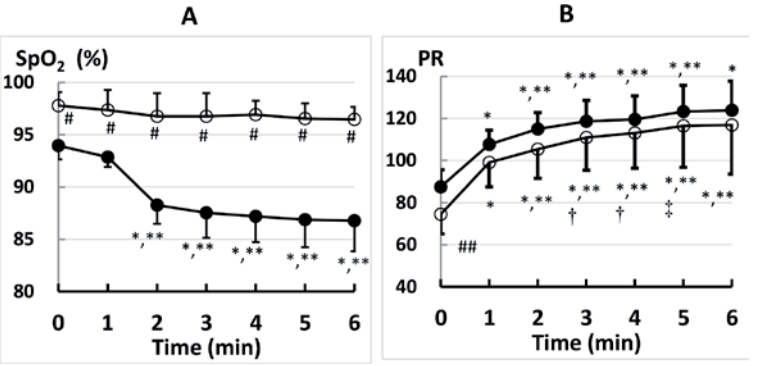


Figure 2.
*Time course changes in SpO_2 (A) and pulse rate (PR) (B) during 6-min walk test. ○: Healthy group, ●: COPD group, Data points are mean ± standard deviation. #: p < 0.01, ##: p < 0.05 against COPD (non-paired t-test), *: p < 0.01 for onset, **: p < 0.01 for 1 min, † p < 0.01 for 2 min, ‡: p < 0.05 for 2 min (intragroup difference, Holm's post hoc test). COPD: chronic obstructive pulmonary disease.*

3.3 COX

Representative recordings of conventional (pre-HMS) and functional (post-HMS) NIRS in a healthy participant (66-year-old) and a patient with COPD (72-year-old) are shown in **Figures 3** and **4**, respectively. In the healthy participant, the conventional NIRS recording showed that Δoxy-Hb and Δtotal-Hb in each channel decreased with the onset of walking, whereas Δdeoxy-Hb slightly increased (**Figure 3A**). Meanwhile, the functional NIRS recording showed a slight decrease in Δoxy-Hb, a slight increase in Δdeoxy-Hb, and no changes in Δtotal-Hb in each channel (**Figure 3B**). In the patient, SpO_2-rest and SpO_2-low were 94% and 87%, respectively. The conventional NIRS recording showed that Δoxy-Hb and Δtotal-Hb in each channel decreased with the onset of walking, whereas Δdeoxy-Hb increased (**Figure 4A**). The functional NIRS recording demonstrated the same trend in each ΔHb, but the amount of change was slightly smaller (**Figure 4B**).

The time course changes in the averages of the functional COX of each group are shown in **Figure 5**. The ANOVA revealed a significant difference in each ΔHb in the groups, lapsed time, and interaction effects. The simple main effects showed a significant difference in each ΔHb (Δoxy-Hb: ($F(6, 72) = 32.627$, $p < 0.01$), Δdeoxy-Hb: ($F(6, 72) = 32.762$, $p < 0.01$), Δtotal Hb: ($F(6, 72) = 32.614$, $p < 0.01$)) in the COPD

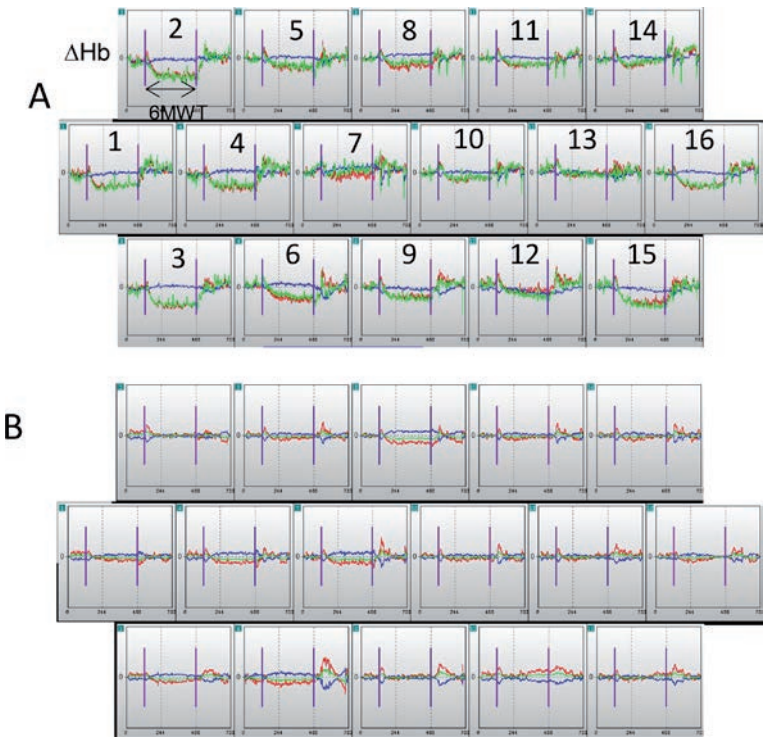


Figure 3.
Representative near-infrared spectroscopy recordings from a 66-year-old healthy participant. A: Conventional recordings (before hemodynamic modality separation), B: Functional recordings (after hemodynamic modality separation). 1–16: forehead channel, red line: oxygenated Hb, blue line: deoxygenated Hb, light green line: total Hb. Hb: hemoglobin.

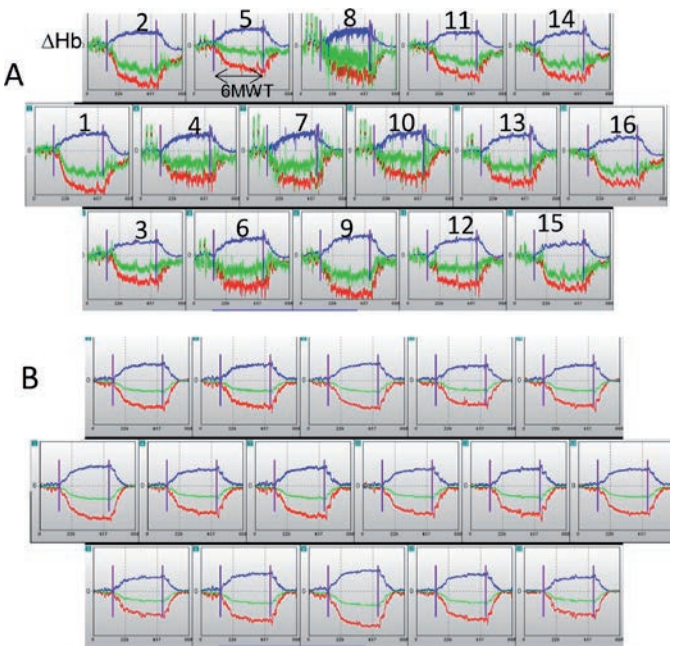


Figure 4.
Representative near-infrared spectroscopy recordings from a 72-year-old patient with COPD. A: Conventional recordings (before hemodynamic modality separation), B: Functional recordings (after hemodynamic modality separation). 1–16: forehead channel, red line: oxygenated Hb, blue line: deoxygenated Hb, light green line: total Hb. Hb: hemoglobin; COPD: chronic obstructive pulmonary disease.

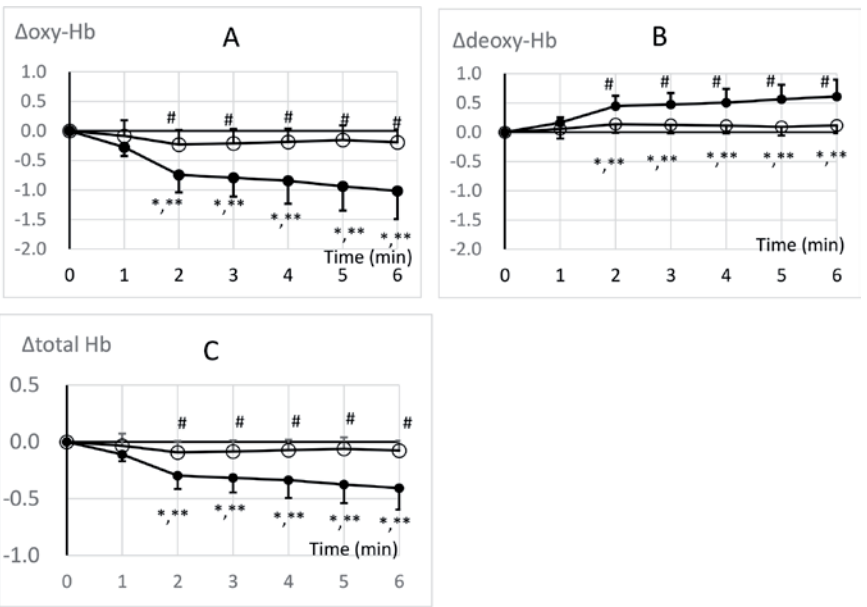


Figure 5.
*Time course changes in Δoxy-Hb (A), Δdeoxy-Hb (B), and Δtotal Hb (C) during 6-min walk test. ○: Healthy group, ●: COPD group, Data points are mean ± standard deviation. Δ signifies change. Oxy-Hb: oxygenated hemoglobin; deoxy-Hb: deoxygenated hemoglobin. #: p < 0.01, against COPD (non-paired t-test), *: p < 0.01 for onset, **: p < 0.01 for 1 min (intragroup difference, Holm's post hoc test).*

group but not in the healthy group. In the COPD group, Δoxy-Hb and Δtotal-Hb were significantly lower at 2 min to 6 min than at the start ($p < 0.01$) and 1 min ($p < 0.01$). Meanwhile, Δdeoxy-Hb was significantly higher at 2 min to 6 min than at the start ($p < 0.01$) and 1 min ($p < 0.01$) (**Figure 5**).

4. Discussion

4.1 Main findings

We investigated the oxygenation status of the frontal lobes of healthy elderly participants and patients with COPD-EIH during the 6MWT to remove the influence of the physiological effect of facial blood flow. The healthy group showed no significant changes in COX during the 6MWT. Meanwhile, the COPD group demonstrated a decrease in Δoxy-Hb and Δtotal-Hb and an increase in Δdeoxy-Hb, suggesting desaturation and hypoperfusion in the frontal cortex during the 6MWT.

4.2 Cerebral oxygenation

Functional COX showed no significant changes in SpO_2 or each ΔHb during the 6MWT in the healthy group. These results suggested that O_2 supply met O_2 demand. The conventional COX during walking in healthy older adults has mostly been studied at a constant walking speed of up to 1 min on a treadmill [27–30]. The results showed that Δoxy-Hb of the prefrontal cortex increased or remained unchanged depending on walking speed and exercise capacity.

The decreased Δoxy-Hb and Δdeoxy-Hb in the frontal lobe among patients with COPD-EIH in the current study suggests desaturation in the frontal lobe. Additionally, the reduced Δtotal-Hb indicates hypoperfusion in the frontal cortex. A previous study found that the exercise intensity of the 6MWT was approximately equivalent to the peak work of ramp cycle exercise in patients with COPD [31]. The findings of our study differ from those of previous studies, which found increased Δoxy-Hb and Δtotal-Hb during high-intensity exercise more than 75% peak workload (WR_{peak}) [14, 16, 17]. However, although these previous studies included patients with EIH, few examined patients with EIH alone. In the previous study by Higashimoto et al. [15], patients with COPD-EIH showed a decrease in Δoxy-Hb from 1 min to 5 min of mild cycle exercise (40% WR_{peak}) and an increase in Δdeoxy-Hb from 3 min, but the Δtotal-Hb increased. This Δtotal-Hb differs from ours, which may be related to differences in the mode and intensity of exercise and the elimination of NIRS signals from skin blood flow.

The possible influencing factors of cerebral blood flow (CBF) during exercise include changes in blood gas tension ($PaCO_2$ and PaO_2), cardiac output, and neuronal activation of the observed brain region [32, 33]. The first, hypercapnia and, to a lesser extent, hypoxia increase CBF by vasodilation, whereas hypocapnia and, possibly, hyperoxia decrease CBF by vasoconstriction [32]. In the present study, Δtotal-Hb was decreased during the 6MWT despite low SpO_2 (85.7 ± 2%). A previous study reported a highly heterogeneous $PaCO_2$ response to 6MWT in patients with moderate-to-severe COPD, with CO_2 retention in 50% of patients, no change in 26%, and a decrease in 24% [34]. Although there was no increase in $PaCO_2$ in the ABG before walking, post-exercise measurements were not performed. Thus, it is unclear whether a decrease or an increase in $PaCO_2$ influences CBF.

Second, the decrease in Δtotal-Hb may be induced by an attenuated increase in cardiac output. Patients with COPD in the current study had no obvious history or symptoms of HF, but cardiac function was not assessed by echocardiography. During submaximal cycle exercise, patients with COPD have more attenuated cardiac output and stroke volume responses than controls [35]. In the study by Oliveira et al. [17], CBF or oxy-Hb did not increase in patients with COPD complicated by heart failure, despite SpO_2 during bicycle exercise at 80% of oxygen uptake being unchanged. Other factors may be related to brain activation. When a region of the brain is activated, Δtotal-Hb and Δoxy-Hb increase in that region owing to an increase in regional CBF [36]. The sensorimotor area and the supplementary motor area are activated during walking [37]. Hence, blood flow allocation to the frontal lobe, which has relatively low neural activity, may be reduced. In contrast, Higashimoto et al. [13] reported that the intensity of dyspnea sensation was associated with increased Δtotal-Hb in the frontal lobe.

The impaired COX after 2 min of maximal speed walking in the current study suggested that the COX during activities of daily living could be impaired in patients with COPD-EIH. In the study by Casanova et al. [5], 22% of patients with COPD moderate hypoxemia (PaO_2 60–70 mmHg) experienced desaturation during the day. Santos et al. [8] reported that the proportion of patients with EIH was higher in real-life telemonitoring than in the 6MWT. The intensity of physical activity that induces COX desaturation should be evaluated in the future. Oxygen administration should be considered not only at rest, but also during daily physical activity with respect to COX.

4.3 Limitations

This study has some limitations. First, the number of patients was small. However, we believe that the COPD group has a larger change in each ΔHb and a larger F value, and that the statistical difference is reliable. Second, the NIRS device used in this study could not measure the absolute concentration of oxy-, deoxy, and total Hb in the brain. Thus, whether the COX at rest was lower in the COPD group than that in the healthy group could not be determined. Finally, this study measured COX only in the frontal lobe. COX in other regions, such as the sensorimotor area, should also be measured during exercise in patients with COPD-EIH.

5. Conclusion

In patients with COPD-EIH, frontal cerebral oxygenation may be impaired after 2 min of walking. Cerebral deoxygenation may be associated with a decrease in SpO_2. The duration and extent of hypoxia in the patients' daily lives should be measured and considered when determining the indication for oxygen administration.

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Author contributions

First Author (Tomoko Kutsuzawa): Conceptualization, Investigation, Formal analysis, Writing-original draft, review & editing; Second Author (Daisaku Kurita); Investigation, Formal analysis; Third Author (Ritsuko Wakabayashi): Investigation, Forth Author (Mayumi Ikeuchi): Investigation, Fifth Author (Munetaka Haida): Methodology, Writing-review & editing.

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Conflict of interest

The authors declare no conflict of interest.

Ethical statement

This study was approved by the Institutional Review Board for Clinical Research, Tokai University (11R-103), and conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data availability statement

Data are available from the corresponding author upon request.

Nomenclature

ABG	arterial blood gas analysis
ANOVA	analysis of variance
BP	blood pressure
CBF	cerebral blood flow
COPD	chronic obstructive pulmonary disease
COX	cerebral oxygenation state
deoxy-Hb	deoxygenated hemoglobin
EIH	exercise-induced hypoxemia
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
Hb	hemoglobin
HF	heart failure
HMS	hemodynamic modality separation
MPAM	multi-distance probe arrangement method
NIRS	near-infrared spectroscopy

oxy-Hb	oxygenated hemoglobin
$PaCO_2$	arterial carbon dioxide tension
PaO_2	arterial oxygen tension
PR	pulse rate
SD	standard deviation
SpO_2	oximetry-measured blood oxygen saturation
VC	vital capacity
WR_{peak}	peak workload
6MWD	walking distance of the 6-min walk test
6MWT	6-min walk test

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Chapter 5

Psychophysical and Social Functioning of COPD Patients: Diagnosis of Comorbid Depression, Modern Principles of Therapy

Ivana Jelic

Abstract

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive and persistent airflow limitation due to a chronic inflammatory response in the airways and lungs induced by noxious particles and gases. The most important risk factors for the development of the disease are smoking, outdoor, indoor and occupational air pollution, infections, and genetic risk. COPD is associated with numerous comorbidities that increase overall mortality. The relationship between depression and COPD is likely bidirectional, as depression can be both a cause and a consequence of COPD, but the exact mechanism of this association remains unclear. Depression is often untreated or insufficiently treated in this group of patients, which worsens health status and quality of life and increases overall mortality.

Keywords: chronic obstructive pulmonary diseases, depression, social functioning, somatic symptoms, quality of life

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive and persistent limitation of airflow, because of a chronic inflammatory response in the airways and lungs triggered by harmful particles and gases. The most significant risk factors for the onset of the disease are smoking, external, internal and occupational air pollution, infections, and genetic risk [1]. COPD is associated with numerous comorbidities that increase overall mortality [2, 3].

The relationship between depression and COPD is most likely bidirectional because depression can be both a cause and a consequence of COPD, yet the exact mechanism of this association remains unclear [4]. These patients may feel useless, have reduced sexual activity, often depend on others for their personal care, lose interest in future events, and regress and focus their energy on their condition [5]. Depression is often untreated or insufficiently treated in this group of patients, which

worsens health status and quality of life and increases overall mortality [6]. In the population of patients with COPD, the subpopulation with associated depression has a significantly higher risk of exacerbation, and therefore, the costs of treating such patients are significantly higher on an annual basis [7].

COPD patients with mild depression benefit from pulmonary rehabilitation and cognitive behavioral therapy, while patients with severe or persistent depression can be treated with pharmacological interventions [8].

1.1 Chronic obstructive pulmonary disease and depression

Symptoms of depression are present even at the time of diagnosis of a chronic illness, accompanied by progressive impairment of physical function and a decrease in quality of life. Mood swings, sleep disturbances, loss of appetite, fatigue, and cognitive impairment are just some of the symptoms of depression that overlap with many other chronic illnesses. Loss of will to live and thoughts about the end of life are symptoms of depression that should be taken seriously and treated promptly. Depression is often unrecognized or undertreated in patients with COPD [9–13].

It ranges from short-term depressive episodes to clinically pronounced depression. Several studies have shown that two-thirds of patients with COPD have moderate to severe depression (e.g., [14–16]). In a 2008 study by Mowrer et al., it was reported that about one quarter of patients with COPD had undiagnosed depression [14].

According to WHO forecasts and the established increased incidence of depression, experts indicate that by 2030 depression will be the most common cause of morbidity in the world [17].

The results of a French study indicate that 41% of patients with chronic illness have either severe depression or, in most cases, it was unidentified and untreated, and in only 6% of cases, psychiatric help was sought [18]. Depression that occurs in comorbidity is often responsible for psychological mechanisms related to the patient's and social perception of the illness [14, 19, 20], but it may also be related to the etiological connection of somatic and psychological illnesses [21–24].

1.2 Prevalence

The prevalence of depression in COPD patients is high, ranging from 10% to 40%. The group of authors conducted a study on 8387 patients with chronic illnesses. The study showed that depression occurs in 26.6% of patients with COPD, and that the majority are older than 55 years. The study lasted 10 years. Controls were performed every other year. The appearance of depressive symptoms after the diagnosis of one of seven chronic diseases, including COPD, was considered. It was noted that 2 years after the diagnosis of COPD, the hazard ratio for the development of depression was 2.21, for cancer 3.55, and for heart disease 1.45 [25].

Depression is most often associated with younger age, female gender, smoking, cough, and cardiovascular disease. In stable COPD, the prevalence of depression ranges from 10% to 42% [26]. Patients with severe COPD, on long-term oxygen therapy (62%), and at home are at particular risk [27].

In patients with exacerbations, the prevalence of depression is higher, ranging from 19.4% to 50% of patients [28, 29]. Some studies estimate the prevalence from 6% to 59%. Post-hoc testing was used to analyze 64 studies that included patients with severe COPD, where the prevalence of depression varied between 37% and 71%

and was higher compared to the prevalence of depression in patients with asthma, cancer, heart disease, and kidney disease [30–32].

Depressive disorders cause more frequent hospitalizations but also increase mortality in patients with COPD. Excessive use of beta2-agonists and corticosteroids as a side effect can manifest these symptoms. A significant number of patients report irritability, stress, and frustration as triggers that cause a feeling of shortness of breath.

1.3 Risk factors for the development of depression in patients with chronic obstructive pulmonary disease

There are numerous risk factors that contribute to the development of depression in these patients. Depression occurs in COPD patients due to their social isolation, physical disability, use of OTC medications, severe dyspnea, low body mass index, poor quality of life, presence of comorbidities, smoking, and current poor social status [33–41].

Patients suffering from depression and COPD are often tobacco users, but it is difficult to determine the extent to which tobacco use affects their disease or diseases. For example, the extent to which people are exposed to tobacco smoke is a matter of quantitative and qualitative assessment. Although qualitative methods rely on data collected from individuals who have previously consumed cigarettes, these methods are limited by ignorance of the question and biases. Biological samples are also used to accurately determine the level of exposure to tobacco smoke [42, 43].

It is believed that an increasing number of female smokers are diagnosed with COPD. Whether there is a relationship between gender and this disease has not yet been established, and several authors have dedicated themselves to researching this issue. For example, in their 2010 study, Serhaimova et al. analyzed the effects of smoking on lung function in 955 subjects with and without COPD [44]. Patients with COPD were divided into two main groups: the first with an early stage and the second with a more advanced stage of the disease. It was found that, compared with men, women had a lower FEV1 percentage and more severe COPD at an early stage. The study found that the effects of cigarette smoking on lung function are different in women compared to men, and that women are more likely to have other diseases, such as diabetes and cancer. The authors concluded that women in the early stages of the disease or with little exposure to tobacco smoke are more likely to have more severe symptoms of the disease, which led them to conclude that gender is a factor contributing to the development of COPD.

It is assumed that in patients with COPD, dyspnea, inactivity, and loss of physical fitness led to even greater inactivity, social isolation, fear, and the onset of depression. Such patients often feel useless, show a strong dependence on others, in terms of caring for their own health and overall life, losing interest in future events, and so on.

1.4 Pathophysiological association of depression and chronic obstructive pulmonary disease

The mechanism of depression in COPD is multifactorial [45]. Although a link between smoking and depression has been described, the underlying mechanism of this association is not fully understood [46]. In some patients, smoking provides relief, but it also increases the chances of developing depression [47]. Smoking leads to oxidative stress, vasomotor and endothelial dysfunction, and increased

concentrations of procoagulant factors in circulation. Increased oxidative stress in the lungs results in inactivation of antiproteases, damage to the airway epithelium, hypersecretion of mucus, increased influx of neutrophils, and proinflammatory mediators (LTB4, IL6, IL8, TNF-alpha, etc.) [48, 49].

The number of inflammatory cells increases in the peripheral blood, especially neutrophils and lymphocytes. This effect is caused by chronic stimulation of bone marrow cells by inflammatory mediators and growth factors (GM-CSF, GCSF). The systemic effects of cigarette smoking may explain the association between COPD and other diseases, primarily depression. Many authors in their studies point to the systemic effects of chronic inflammation and report that smoking has a strong anxiolytic effect on patients with chronic inflammation previously explained by a pathophysiological mechanism (e.g., [50, 51]).

There is increasing evidence that systemic inflammation leads to depression. Interleukin-6 (IL-6) has a particularly important role in humans. IL-6 is increased in sputum, exhaled air, and plasma of patients with COPD, most pronounced during exacerbations. IL-6 concentration is directly related to increased levels of C-reactive protein (CRP), and it is also the main stimulator of CRP release from the liver. Unlike other cytokines, IL-6 is stable in circulation and is considered responsible for additional systemic effects of chronic disease. It has been shown to contribute to endothelial cell dysfunction, insulin resistance, osteoporosis, and depression in COPD patients [52–55].

1.4.1 Assessment of depression in chronic obstructive pulmonary disease

Mood disorders have a high comorbidity potential, more than other mental or physical illnesses. For these reasons, more attention has been paid to screening programs in primary health care, although no "screening" or diagnostic instrument for assessing depression in COPD has been developed in our country so far. The most used instruments are the Beck Depression Inventory and the Hamilton Depression Inventory (e.g., [56, 57]). In this study [58], the Hamilton Depression Inventory was used as a diagnostic instrument for assessing the degree of depression.

According to the 2015 GOLD guidelines [59], a detailed medical history should be taken from every newly diagnosed patient, including an assessment for depression [60].

The 2017 WHO recommendations emphasize the importance of screening all patients over 18 years of age in primary care for depression. This includes all chronic patients [61].

There are various barriers to detecting depression in patients with chronic obstructive pulmonary disease, both from the patient and the physician perspective. The most common barrier for patients is the "stigma" that exists about mental illnesses, resistance to revealing symptoms, and lack of knowledge about the diseases. Doctors are increasingly emphasizing the importance of educational counseling centers, believing that through education they will bring patients closer to the importance of preventive examinations and thus reduce the level of mental disorders [61, 62].

1.4.2 Measuring quality of life: Before and after the use of antidepressants

According to a study by Johannes and Connolly from 2011, patients with COPD often avoid taking antidepressants due to various prejudices. This includes the stigma

associated with depression and the belief that it causes addiction. What is considered important is the fact that health professionals should be educated on how to properly diagnose and treat depression in patients with COPD [63]. Compared with other drug therapies, antidepressants have been shown to be safer and more effective when used to treat depression in patients with COPD [63]. These authors report in their paper that several studies have been conducted on the use of antidepressants in patients with this disease [63]. Studies have shown that quality of life in patients with COPD with comorbid depression improved after 6 and 12 weeks [64, 65].

In a study by Jelić et al., published in 2023 [66], the authors examined the effects of antidepressant therapy in patients with COPD and depressive disorder in relation to the levels of that disease. Patient characteristics are presented in **Table 1**. Antidepressant therapy lasted for 8 weeks, and the results showed a significant improvement in quality of life in patients after the use of antidepressants, which was measured using the HAM-D scale [67].

Although research on the efficacy of antidepressants for the treatment of depression in patients with COPD is not widespread, existing research suggests that antidepressant therapy may improve quality of life in these patients. Findings from the literature presented are largely limited by methodological shortcomings, such as small sample sizes and heterogeneity, variations in diagnostic instruments used to measure and monitor depression treatment, and the like. Certainly, the appropriateness of using antidepressants for the treatment of depression in patients with COPD requires further and more detailed research. In recent years, researchers have devoted much attention to studies examining the association of somatic diseases with comorbidities and therapeutic monitoring. The aim of the study Jelic et al. [67] was to determine the relationship between the degree of COPD, the degree of depression, and the quality of life and life satisfaction of patients with COPD and depressive disorder before and after antidepressant therapy (**Table 2**).

Using the same number of patients as in this study Jelic et al. [66], Khan and Patil [68] examined the prevalence of depression in patients with COPD according to the GOLD 2015 criteria [59]. In contrast to this study, Khan and Patil [68] used Beck's depression score to assess depression. According to the findings of these authors, 18 patients were in the GOLD-1 stage, GOLD-2 included 66 patients, GOLD-3–29 patients, and GOLD-4–7 patients.

In the study [69], the authors examined the quality of life of patients with chronic mental illnesses, who were divided into three groups: 69 patients with schizophrenia, 37 with bipolar disorder, and 35 with major depression. To assess the difference in quality of life between these three groups of patients, as well as the difference

Characteristics	
Sex	
Male	34.5%
Female	65.5%
Age (mean ± SD)	48.84 ± 7.43
HAM-D1 score before AD therapy (mean ± SD)	20.23 ± 5.072
HAM-D2 score after AD therapy (mean ± SD)	11.37 ± 5.786

Table 1.
Characteristics of study patients.

Domains		Overall life satisfaction after AD therapy			p
		Poor	Fair	Good	
Level dyspnea	1	0 (0.0%)	26 (21.7%)	17 (14.2%)	F = 21.263, p = 0.000
	2	0 (0.0%)	51 (42.5%)	6 (5.0%)	
	3	1 (0.8%)	19 (15.8%)	0 (0.0%)	
Total		1 (0.8%)	96 (80.0%)	23 (19.2%)	
Level depression	0	0 (0.0%)	23 (19.2%)	19 (15.8%)	F = 32.077, p = 0.000
	1	0 (0.0%)	54 (45.0%)	4 (3.3%)	
	2	1 (0.8%)	17 (14.2%)	0 (0.0%)	
	3	0 (0.0%)	2 (1.7%)	0 (0.0%)	
Total		1 (0.8%)	96 (80.0%)	23 (19.2%)	

Table 2.
Overall life satisfaction in patients after AD therapy in relation to the level of dyspnea and level of depression according to Q-LES-Q-SF scores.

between self-assessment (subjective responses) and professional assessment (objective responses), they used the quality-of-life index (QoL). In relation to patients diagnosed with major depression, the difference in the results of the assessment and self-assessment is large. Patients with severe depression rated their quality of life even significantly lower than patients with schizophrenia, which is contrary to the results of objective indicators of quality of life. Therefore, these authors questioned the validity of self-assessment measures, especially in patients with affective disorders, because the results can be influenced by affective bias, poor perception of reality, recent life events, and other similar circumstances that prevent a more accurate insight into the real state. Based on this, it is considered that for the assessment of quality of life in patients with affective disorders, that is, in patients with depressive disorders, a more adequate professional role is considered, i.e., that the examination is performed by a psychiatrist/neuropsychiatrist, which is also agreed with by Miljković, Vukić and Trajanović [70].

The relationship between clinical symptoms HOBP and quality of life is an important issue to be addressed in the treatment of COPD. Depressive symptoms indirectly affect the environment and social quality of life and are often associated with various, interrelated factors, such as work capacity, employment status, living situation, and quality of social relationships, the improvements of which most often occur later in relation to symptom reduction [71–76]. For example, in a study [77] it was found that women with COPD, in addition to being more prone to depression, also showed worse symptoms in variables related to quality of life. According to the results of the study [78], the quality of life of patients with COPD and comorbid depression improved with the additional treatment with aripiprazole. After this therapy, a decrease and a positive change in physical and psychological quality of life were shown. In other words, the improvement in functioning affected all domains of quality of life. In the study by Jelić et al. [67], it was also found that after antidepressant therapy, patients had positive results. Namely, the physical condition that was recorded as poor before antidepressant therapy was now significantly reduced after therapy (**Table 3**). When it comes to the positive outcome of antidepressant therapy in patients with COPD with comorbidity of depression, the results of this study are in line with previous

Overall life satisfaction before AD therapy	Overall life satisfaction after AD therapy	p*
2.19 ± 0.397	3.18 ± 0.410	p = 0.000

**Wilcoxon signed-rank test.*

Table 3.
Overall life satisfaction before and after AD therapy.

studies, such as [55, 75]. Namely, in the treatment of these patients, medications were used to normalize the symptoms of depression, which were shown to have a statistically significant impact on their quality of life.

Analyzing the comorbidities of the subjects, Antonelli et al. [79] found that almost half of the patients with COPD had comorbidities. Namely, out of 270 patients with COPD, 28% of them had hypertension, 14% diabetes, and 10% coronary artery disease [69]. The authors of the study [38, 68] noted the frequency of the presence of depression in relation to anxiety in patients with COPD. Similarly, Miravitlles's et al. found that 74.6% of patients with stable COPD had depression in a sample of 836 patients in Spain [80].

Sociodemographic and psychological relationships characterize the environment in which patients live, work, and establish contacts with others to ensure the support of the global society to which they belong. Their impact on the quality of life of the patient is still being studied. Given that the goal of modern therapeutic procedures is to improve the quality of life of patients with somatic diseases and comorbidities, research on the quality of life of patients has begun. The results of many studies indicate that all categories of health are associated with a lower quality of life, and that they influence each other.

In the last 20 years, significant progress has been made in the field of diagnosing the quality of life of patients. To successfully determine quality of life, it is necessary to make a good choice of test that provides high sensitivity and specificity, but also the speed of the test, which, according to the recommendations of the European and American Centers for Disease Control (ECDC and CDC), are nucleic acid amplification tests.

Unfavorable socioeconomic status is now accepted as a clear risk factor for the development of COPD, although the components of poverty that contribute to this have not been fully established. In this study Jelic et al. [66] respondents rated their economic status and material situation as bad and very bad. Also, sexual drive/interest is associated with depression, which is confirmed in this work and is in line with previous research (e.g., [77]). It was also found that sexual drive/interest was rated as poor in 85.3% of men, but also in women, before antidepressant therapy, while after antidepressant therapy, the results were different. Namely, sexual drive/interest was rated as poor in 82.2% of men, indicating an improvement, while it was rated as poor in 86.7% of women (which is a deterioration of 1.4%). The presented result has also been proven in population studies that study these diseases, such as in the study [77], where the authors believe that women are at greater risk, because many of them, in addition to doing housework, tend to live alone or take care of the elderly. In addition to all the above, cigarette smoking is cited as the main risk factor for the development of this disease, although only 20% of smokers develop this disease. This clearly indicates the need to identify other risk factors and to pay special attention to them when examining the development of COPD, precisely because they have been neglected in previous years. Undiagnosed, and consequently untreated, depression can lead to

serious complications, especially in women. Clinical manifestations of depression in women primarily include withdrawal, despondency, loss of will and energy, insomnia, loss of appetite, indulging in dark thoughts, hopelessness, and helplessness. In some cases, spontaneous resolution of the degree of depression occurs, while in some women it can lead to serious mental impairment and complications such as suicide. In men, depression mainly leads to feelings of hopelessness, failure, family dysfunction, and decreased work capacity. For these reasons, many countries implement various programs for the control and prevention of depression. Depression control programs are largely based on screening for asymptomatic depressive episodes in people of both sexes. These programs are expected to reduce the consequences of depression that harms people's mental health, as well as to further prevent the spread of mental disorders.

2. Conclusion

The high frequency of asymptomatic depression, as well as the possibility of adverse mental health outcomes, have encouraged the development of more sensitive instruments and tools for assessing and measuring symptoms of depression. Early diagnosis of depression is extremely important, but also very challenging due to the asymptomatic nature and characteristic developmental cycle of the disease itself. Timely diagnosis and recognition of the systemic effects of the disease itself contribute to better monitoring of its course, more effective treatment, and a better quality of life.

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Chapter 6

The Impact of Non-pharmacological Interventions in Reducing Hospitalizations for Non-COVID Respiratory Illnesses during COVID-19

Kian Chung Ong

Abstract

Throughout the coronavirus disease (COVID-19) pandemic, non-pharmacological interventions—including social distancing, reinforcement of hygiene practices, and the mandatory use of face masks—were adopted as precautionary strategies to mitigate the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These measures demonstrated effectiveness in reducing viral spread, even before the development of passive or acquired immunity in the community. The widespread implementation of these interventions also led to significant changes in the case-transmission and hospitalization rates of non-COVID respiratory infections caused by established respiratory pathogens. Furthermore, disproportionate declines in hospitalization rates of non-COVID respiratory illnesses such as chronic obstructive pulmonary disease were reported from many countries during the pandemic, supporting the long-held belief that respiratory viral infections are largely responsible for exacerbation of chronic obstructive pulmonary disease, and that the non-pharmacological interventions adopted during the pandemic can effectively reduce the hospitalization rates of this major illness. While further research is required to confirm the type and effectiveness of preventive interventions in reducing the hospitalization rates of respiratory diseases, observational data from the COVID-19 pandemic present a considerable case for advocating some ongoing measures of infection control aimed at reducing hospitalization for patients with chronic lung diseases and those at high risk of developing community-acquired pneumonia.

Keywords: prevention, admissions, respiratory virus, pandemic, disease burden, respiratory infection, chronic obstructive pulmonary disease

1. Introduction

The global pandemic caused by SARS-CoV-2 (COVID-19) began in December 2019 and after more than 2 years of untold mortality and suffering, it rescinded to

less than a public health emergency in May 2023. In the initial phase of the pandemic, non-pharmacological interventions (NPIs), including mask usage and physical distancing, served as the sole methods of infection control. While these measures were unequivocally effective in lowering COVID-19 transmission rates prior to the development of passive or acquired community immunity, NPIs also produced several less expected benefits, such as reducing the burden of non-COVID-19 infections and noncommunicable diseases on the severely stretched global healthcare system. One major respiratory condition that observed a welcome decline in hospitalizations when NPIs were implemented early during the pandemic in 2020 was exacerbation of chronic obstructive pulmonary disease (COPD).

Even prior to the COVID-19 pandemic, COPD was the third leading cause of mortality worldwide and major expenditures of healthcare budgets across the globe have been apportioned to hospitalization for exacerbation of COPD, which may be defined as an acute worsening of respiratory symptoms that warrants additional therapy [1]. About 50% of cases of exacerbation in COPD have been attributed to respiratory viral infections [2]. Accordingly, when COVID-19 started, the fear was an impending surge in hospitalization of COVID-19-related respiratory illness such as COPD exacerbations. This initial anxiety was unfounded as multiple centers worldwide subsequently reported dramatic reductions in hospitalizations for COPD starting in 2020, most possibly attributed to universal implementation of NPIs.

Retrospectively, the COVID-19 pandemic has thus provided a 'natural experiment' in evaluating the overall impact of NPIs on healthcare-resource utilization of COPD and other respiratory illnesses. The aim of this publication is to provide a narrative review of the impacts of implementing NPIs during the pandemic, with a view toward future applications in reducing disease burden borne by exacerbation of COPD and outbreaks of community-acquired pneumonia (CAP).

2. Types of NPI

NPIs were important strategies in preventing or reducing viral transmission during the pandemic. Based on the typical progression of COVID-19, preventive measures during the pandemic can be classified into three levels: (1) primordial and primary prevention—targeting the environmental and social determinants that contribute to disease onset and aiming to prevent infection in healthy individuals; (2) secondary prevention—focused on early identification and management of subclinical cases among asymptomatic or pre-symptomatic individuals; and (3) tertiary prevention—aimed at mitigating disease severity and minimizing complications in those already infected [3, 4]. The rest of this article will only discuss the use of NPIs for the purpose of primordial, primary, and secondary prevention during the pandemic, as in-depth reviews of NPIs for tertiary and quaternary prevention in healthcare settings are available elsewhere [3]. The near-simultaneous global implementation of NPIs in community settings since the onset of the pandemic is summarized in **Table 1**.

3. Impact on respiratory infections: Viral and pneumococcal

From 2020, with the punctiliar global implementation of NPIs in community settings, reductions in community respiratory virus activity have been reported in many countries. Among the non-SARS-CoV-2 respiratory viruses, the impact of NPIs

Category	Examples & descriptions
Individual/Personal Level	
Wearing face masks	Used by infected individuals to reduce transmission, and by others for protection.
Respiratory social etiquette	Cover coughs and sneezes (without using hands) to reduce spread of droplets.
Hand hygiene	Wash hands with soap and water, or use alcohol-based sanitizers.
Physical distancing	Keep at least 2 meters apart from others; avoid crowded spaces.
Screening & isolation of symptomatic individuals	Separate unwell persons at home, school, or workplace; often combined with testing.
Quarantine of exposed cases	Require or encourage exposed persons to stay home, monitor symptoms, and undergo testing.
Community Level	
Mask mandates in public	Enforce mask-wearing in enclosed public areas and on public transport.
Closure of schools & childcare facilities	Suspend in-person learning; shift to remote or online education.
Restrictions on gatherings & events	Limit or cancel large events, especially indoors.
Stay-at-home/lockdown measures	Defer non-essential services, restrict community movement, support telework, and encourage delivery services.
Contact tracing	Identify, test, and quarantine close contacts; prioritize treatment for high-risk cases.
Reduced public transport use	Limit access to or reduce availability of public transit.
Public health communication	Share information through various channels and social media.
Community surveillance	Conduct routine testing and monitoring in targeted groups or areas.
Environmental Level	
Improving indoor air quality	Upgrade ventilation and filtration systems; use portable filters, UV disinfection, fans, and open windows.
Surface disinfection	Regularly clean high-touch surfaces such as doorknobs, toys, desks, and bathroom fixtures.
National/Country Level	
Border restrictions	Limit or close international travel and cross-border movement.
Health screening at entry/exit points	Detect potentially infected travelers before crossing borders.
Traveler quarantine	Require incoming travelers to undergo quarantine.
Travel regulations & advisories	Issue alerts for high-risk destinations; require negative tests, vaccination proof, or mask use on flights.

**Adapted from Reference [4].*

Table 1.
*Community non-pharmaceutical interventions used during the COVID-19 pandemic**

on community circulation of influenza virus and respiratory syncytial virus (RSV), the two commonest viruses included in routine surveillance, is well documented [4]. The implementation of NPIs in the early stages of the COVID-19 pandemic led to a

substantial decline in global influenza activity, and similarly, case numbers of RSV showed a significant reduction across diverse geographic regions and climate zones [4]. Although tempting to attribute reductions in non-SARS-CoV-2 activity solely to the globally synchronized use of NPIs, it must be noted that other postulations for these widespread observations exist. One plausibility is the direct or indirect antagonistic viral interaction that may account for reduced likelihood of developing another viral infection when a host is simultaneously or sequentially exposed to more than one respiratory virus. Together with influenza virus and RSV, the circulation of other non-SARS-CoV-2 respiratory viruses, including parainfluenza virus, seasonal human coronaviruses, and human metapneumovirus, declined markedly at the onset of the pandemic following the implementation of NPIs. Nonetheless, certain endemic respiratory viruses, such as rhinoviruses, adenoviruses, and respiratory enteroviruses, continued to circulate, despite widespread community-based interventions [4]. It has been postulated that inherent properties of these viruses, such as their lack of viral envelopes and their environmental stability, might have led to their persistence, despite implementing NPIs. Among non-SARS-CoV-2 respiratory viruses causing non-COVID-19 CAP during the pandemic, there were marked reductions in both incidence and diversity of viruses, with only rhinovirus-associated CAP reported as a persistent and lingering viral cause of non-COVID-19 CAP in 2020 [5].

It may be easier to attribute the published global decline in invasive pneumococcal disease (including pneumonia) to *Streptococcus pneumoniae* to the downstream effects of NPIs [4]. This is so as co-infections of *S. pneumoniae* and SARS-CoV-2 were uncommon during the pandemic and the incidence of invasive pneumococcal disease rebounded when NPIs were removed [4].

3.1 Tuberculosis

In a study comparing the rates of mortality due to tuberculosis (TB) during the pandemic with corresponding mortality rates in the pre-pandemic era (from 2016 to 2019) in several countries, it was observed that TB mortality rates had generally risen [6]. The authors opined that this trend was attributable to disruptions in access to tuberculosis services and the reallocation of resources away from these programs [6]. The World Health Organization (WHO) also reported that global TB deaths have increased for the first time in a decade, reversing years of global progress tackling TB [7]. On a positive note, near-universal NPIs, such as the enforcement of mask-wearing and other mandatory measures during the pandemic, contributed to normalizing their use against airborne infectious diseases, including TB, while also reducing associated stigma. As pandemic restrictions ease and adherence to such measures becomes less rigorous, it remains critical that infection-control behaviors and the destigmatization of mask use be sustained in the context of TB care. This is particularly relevant in low-income countries with high TB prevalence, where compliance with NPIs—such as the use of personal protective equipment by healthcare workers and mask use among patients—has historically been limited [6, 7].

4. Impact on non-COVID-19 respiratory illness (NCRI) and non-respiratory illnesses

In the early phase of COVID-19-related NPI implementation, a parallel decline was observed in hospitalizations for non-COVID-19 conditions. During the initial

months of the pandemic, this global reduction in healthcare utilization was likely driven in part by concerns over nosocomial transmission of COVID-19, and in part by the suspended treatment of nonemergent cases. However, in many centers in Canada, it was noted that hospitalization for non-COVID-19 respiratory illnesses (NCRIs) surprisingly dwindled, despite a rebound in non-respiratory conditions, e.g., gastrointestinal and cardiac conditions, months into the pandemic. Hospitalization rates for gastrointestinal and cardiac conditions decreased 13 and 14%, respectively, compared to pre-pandemic levels in 2020, while hospitalization rates for two NCRIs—COPD and non-COVID-19 pneumonia decreased by 38 and 36%, respectively, in 2020 [8].

This decreased burden of NCRIs subsequently became recognized as a worldwide phenomenon as reports and meta-analyses emerged from numerous regions internationally [8]. The first report of the reduction effect of COVID-19 on the hospitalization rate of exacerbation of COPD was from a single center in Singapore [9]. Patients admitted with suspected virus-induced exacerbations of COPD, who underwent testing for respiratory viral pathogens using a 16-target multiplex Polymerase Chain Reaction (PCR) assay (RV-16) on respiratory specimens, were evaluated over a six-month period (February to July 2020) and compared with cases from the 2-year pre-pandemic period (January 2018 to January 2020). In the post-pandemic period, monthly COPD admissions declined by approximately 50% compared to pre-pandemic levels—an impressive effect hardly matched by conventional treatment modalities in reducing exacerbation frequency. While part of this reduction may be explained by patients' reluctance to seek hospitalization during the pandemic, a marked decline in PCR-confirmed respiratory viral infections among COPD admissions was also observed, despite heightened vigilance in testing. Prior to the pandemic, nearly half of COPD admissions tested positive for a respiratory viral pathogen (48.8%), compared with only 10.8% during the pandemic [9]. Another study published in 2022 [10] also reported dramatic reductions in monthly COPD admissions during the first year of the pandemic in Germany, and the declines in COPD hospitalizations seemed disproportionate compared to hospitalization rates of other major comorbidities such as myocardial infarction and stroke—another piece of observational data that refutes the hypothesis that reductions in COPD admissions during the pandemic are due to a general trend in avoiding hospitalization.

A meta-analysis evaluating COPD admissions data from nine countries during the pandemic found that the overall hospitalization rate was 50% less than that during pre-pandemic times [11]. In this systematic analysis, it was also observed that there was no significant correlation between the COVID-19 Containment and Health Index and the reduction in COPD exacerbations across countries, suggesting that individual patient behaviors may have exerted a greater influence than population-level policy measures [11].

Since NPIs are effective in limiting the transmission of viral pathogens, the primary identified triggers of acute respiratory infections as well as exacerbations of chronic airway diseases such as COPD [1, 2], such data strongly postulate that the NPIs implemented during COVID-19 are effective in preventing the spread of, not just SARS-CoV-2, but also established respiratory viruses. The remote possibility of other risk factors for COPD exacerbation such as air pollution also being decreased during the pandemic (e.g., small particulate matter levels were shown to be reduced in some locations during the COVID-19 pandemic) seems a lot less likely, given the observed sequential 'off-on' phenomena of the fall/winter seasonality of COPD exacerbations that were disrupted (for the first time) during the pandemic and swiftly reestablished after the pandemic [12].

5. Future implications

Further research is required to analyze the observed benefits of NPIs, and this should be carried out using time-series analyses that may help clarify whether specific NPIs exert differential impacts and identify which interventions are particularly effective in preventing transmission of viruses [12]. The preliminary data of a time-series analysis are currently available [12]. Using an interrupted time-series analysis, the decline in COPD exacerbations coincided with the implementation of infection-control measures, while the resurgence of seasonal viruses paralleled the return of exacerbations, thereby reinforcing the role of viral infections in precipitating COPD exacerbations [12]. These observational data are so convincing that the authors have invoked such data to call for the adoption of individual protective measures during winter by patients with COPD, as well as by their relatives and caregivers [12].

Predominant viral triggers may vary according to disease type and patient demographic characteristics, and further analyses of observed data can support the need for more targeted NPIs tailored to specific population subsets. Additionally, current evidence suggests that certain NPIs like wearing face masks against COVID-19 are more efficacious in a source control strategy (mask-wearing by infectious people) rather than as personal protective equipment [8]. Randomized controlled trials (RCTs) are necessary to determine whether the benefits of NPIs can be sustained when applied to specific patient groups, or on voluntary bases only rather than when enforced across the population level. As robust evidence from RCTs may require years to acquire, the highly positive effect of NPIs on reducing the burden of NCRIs such as COPD and CAP as described above should prompt deliberation on whether mask use is appropriate for patients with chronic lung diseases, individuals at elevated risk of developing CAP, and those in close contact with them [8]. A previous study evaluating the acceptability of physical interventions (hygiene, face covering, and social distancing) to people living with airways diseases such as COPD, asthma, and bronchiectasis found that they were supportive of some ongoing infection-control interventions to prevent exacerbations beyond the pandemic, and the authors recommended that such measures be considered in future treatment guidelines [13]. Such novel measures could potentially reduce the high burden of hospital re-admissions for COPD exacerbations, and abet the prevention of such episodes, a task that has been identified as a top priority by patients and clinicians in a research prioritization exercise [14].

Finally, as with any medical intervention, the potential benefits of NPIs should be weighed against possible drawbacks such as selecting out of virulent viral illnesses like RSV or influenza or of non-enveloped viruses that are more resistant to effects of masking. NPIs may also incur huge socioeconomic costs and negatively impact individuals' psychological well-being. Nonetheless, until firm recommendations regarding the appropriate post-pandemic use of NPIs are established, observational data from COVID-19 support the use of NPIs, especially on a voluntary basis, to protect at-risk individuals.

6. Conclusion

Examining the changes associated with NPI implementation during the COVID-19 pandemic may enhance our understanding of the interviral dynamics that regulate

community co-circulation and shape public health recommendations in mitigating infection contributing to hospitalizations for major respiratory diseases, such as COPD and CAP.

Conflict of interest

The author declares no conflict of interest.

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Chapter 7

Artificial Intelligence in Pulmonary Hypertension: Advancing Early Detection, Risk Stratification, and Therapeutic Decision-Making

Reza Eshraghi, Mohammad Sepehr Yazdani and Ashkan Bahrami

Abstract

Pulmonary hypertension (PH) constitutes one of the major global reasons for mortality and morbidity. PH is a complicated and gradually aggressive disorder. The heterogeneous nature of PH makes its diagnosis, risk assessment, and treatment all the more complex. The present chapter addresses the utilization of AI in finding and personalized management of PH. AI-based methods analyze several kinds of data, including cardiac auscultation, electrocardiography (ECG), chest radiography, echocardiography, computed tomography (CT), and cardiac magnetic resonance (CMR) imaging. AI algorithms could enhance diagnostic accuracy by detecting PH earlier, forecasting disease progression and treatment response, and assisting with risk stratification. By integrating comprehensive patient data, such as clinical, genetic, and molecular information, AI assists in the development of personalized treatment plans.

Keywords: pulmonary hypertension, artificial intelligence, machine learning, early detection, diagnostic imaging, risk stratification, personalized medicine

1. Introduction

Pulmonary hypertension (PH) represents a variety of health conditions defined by elevated pulmonary artery blood pressure, specifically a mean pulmonary arterial pressure (mPAP) over 20 mm Hg [1]. A greater probability for mortality is clearly linked to elevated mPAP [2, 3]. However, pulmonary vascular disease cannot be adequately distinguished from other explanations of increased pulmonary pressure, such as increased cardiac output (CO) or elevated left ventricular filling pressures, using mPAP alone without a full set of hemodynamic measurements obtained *via* right heart catheterization (RHC).

The 6th World Symposium on Pulmonary Hypertension (WSPH) states that there are two main categories for PH: hemodynamic categorization and clinical categorization [4]. Five categories are used by WSPH: (1) pulmonary arterial hypertension (PAH), (2) PH due to left heart disease, (3) hypoxia-related PH in patients with

lung diseases, (4) PH is linked to persistent blockage of the pulmonary arteries, and (5) PH, whose causes are not well understood or involve more than one factor [4] (**Table 1**). For precapillary PH, the following criteria must be met: (1) mPAP of 20 mm Hg or higher, pulmonary wedge pressure (PAWP) of 15 mm Hg or lower, and pulmonary vascular resistance (PVR) of at least two Wood units. (2) In the case of isolated postcapillary PH, the following conditions must be met: mPAP exceeding 20 mm Hg, PAWP greater than 15 mm Hg, and PVR at or below 2 Wood units. (3) The mixed precapillary and postcapillary PH is as follows: mPAP exceeding 20 mm Hg,

PAH	Idiopathic PAH		
	Heritable PAH		
	Drug- and toxin-induced PAH	Aminorex, Fenfluramine, Dexfenfluramine, Benfluorex, Methamphetamines, Dasatinib, Toxic rapeseed oil	
	PAH associated with	Connective tissue disease	
		HIV infection	
		Portal hypertension	
		Congenital heart disease	
		Schistosomiasis	
	PAH long-term responders to calcium channel blockers		
	PAH with overt features of venous/capillaries (PVOD/PCH) involvement		
	Persistent PH of the newborn syndrome		
PH due to left heart disease	PH due to heart failure with preserved LVEF		
	PH due to heart failure with reduced LVEF		
	Valvular heart disease		
	Congenital/acquired cardiovascular conditions leading to postcapillary PH		
PH due to lung diseases and/or hypoxia	Obstructive lung disease		
	Restrictive lung disease		
	Other lung disease with mixed restrictive/obstructive pattern		
	Hypoxia without lung disease		
	Developmental lung disorders		
PH due to pulmonary artery obstructions	Chronic thromboembolic PH		
	Other pulmonary artery obstructions	Sarcoma (high or intermediate grade) or angiosarcoma	
		Other malignant tumors Renal carcinoma Uterine carcinoma Germ cell tumors of the testis Other tumors	
		Non-malignant tumors Uterine leiomyoma	
		Arteritis without connective tissue disease	
		Congenital pulmonary artery stenoses	
		Parasites Hydatidosis	

PH with unclear and/or multifactorial mechanisms	Hematologic disorders	Chronic haemolytic anemia
		Myeloproliferative disorders
	Systemic and metabolic disorders	Pulmonary Langerhans cell histiocytosis
		Gaucher disease
		Glycogen storage disease
		Neurofibromatosis
		Sarcoidosis
	Others	Chronic renal failure with or without hemodialysis
		Fibrosing mediastinitis
	Complex congenital heart disease	[5]

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

Table 1.
Recent clinical evaluations for PH.

Definitions	Characteristics	Clinical groups#
Precapillary PH	mPAP more than 20 mmHg	PAH, PH because of lung disease and/or hypoxia, PH because of pulmonary artery obstruction and PH with unclear and/or multifactorial mechanisms.
	PAWP less than or equal to 15 mmHg	
	PVR more than or equal to 3 WU	
Isolated postcapillary PH (IpcPH)	mPAP more than 20 mmHg	PH because of left heart disease and PH with unclear and/or multifactorial mechanisms.
	PAWP more than 15 mmHg	
	PVR less than 3 WU	
Combined pre- and postcapillary PH (CpcPH)	mPAP more than 20 mmHg	PH because of left heart disease and PH with unclear and/or multifactorial mechanisms.
	PAWP more than 15 mmHg	
	PVR more than or equal to 3 WU	

WU: Wood Units

Table 2.
Hemodynamic definitions of pulmonary hypertension (PH).

PAWP exceeding 15 mm Hg, and PVR exceeding 2 Wood units (**Table 2**). In **Figure 1**, the biological process of pulmonary vascular remodeling in PAH is demonstrated.

When it comes to diagnosing PH, RHC represents the gold standard [7]. Because of the restricted predictive utility of RHC in some PH groups, particularly in cases where PH-targeted treatments are not required [8], non-invasive assessments as well as analysis of these results tend to be more important. Additional restrictions on

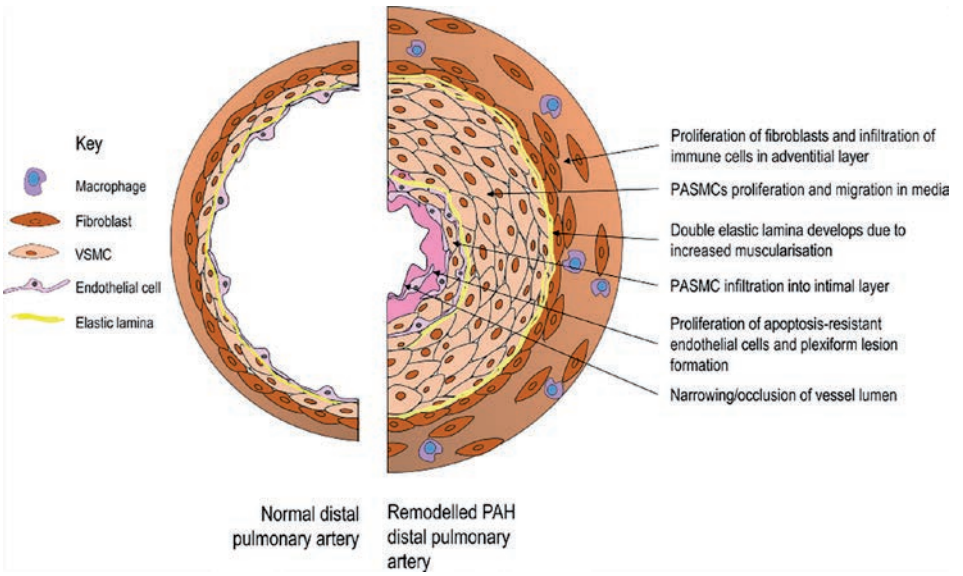


Figure 1.
The diagram depicts a cross-section of a small pulmonary artery, pointing out the biological process of pulmonary vascular remodeling in PAH. The resulting modifications to the structure cause to the narrowing or total blockage of the vessel's lumen. Functionally, this remodeling worsens blood pressure inside the fundamentally low-pressure circulatory system, amplifying the workload demanded of the right ventricle. Reproduced from Morris Hannah et al. [6] under the terms of the Creative Commons Attribution License (CC BY).

RHC as the gold standard test for PH include: (1) hemodynamic concepts do not have uniform guidelines for challenging events for assessing the vascular response and rely on a single time point evaluation. (2) An overall absence of precision hinders the identification of appropriate preload over RHC. (3) The precision and reliability of PAWP estimates throughout the respiratory process are susceptible to error [9]. The efficiency and popularity of AI in healthcare have significantly increased in recent years, particularly due to advances in machine learning (ML) techniques that enable automated analysis of complex medical data.

The term AI refers to a broad category of software algorithms that can carry out functions that would normally require someone with intelligence. A branch of AI called machine learning (ML) uses feature-based learning rather than clear instructions to develop programs to resolve problems. A particular type of ML called deep learning (DL) extracts characteristics by using various levels. One type of DL which is partially modeled after synapses in our own nervous system, is 'convolutional neural networks' (CNNs). Numerous layers contain a number of 'nodes', and every 'node' receives a value as a data point that influences the entire 'network'.

Since AI is being used more and more in many fields, especially medicine, we plan to concentrate on its applications in PH in this chapter including its use in diagnosis, treatment, and research.

2. AI in pulmonary hypertension: Detection and diagnosis

In **Figure 2**, we illustrated the integration of multiple clinical data sources, including cardiac auscultation, ECG, chest X-ray, echocardiography, CT, and CMR

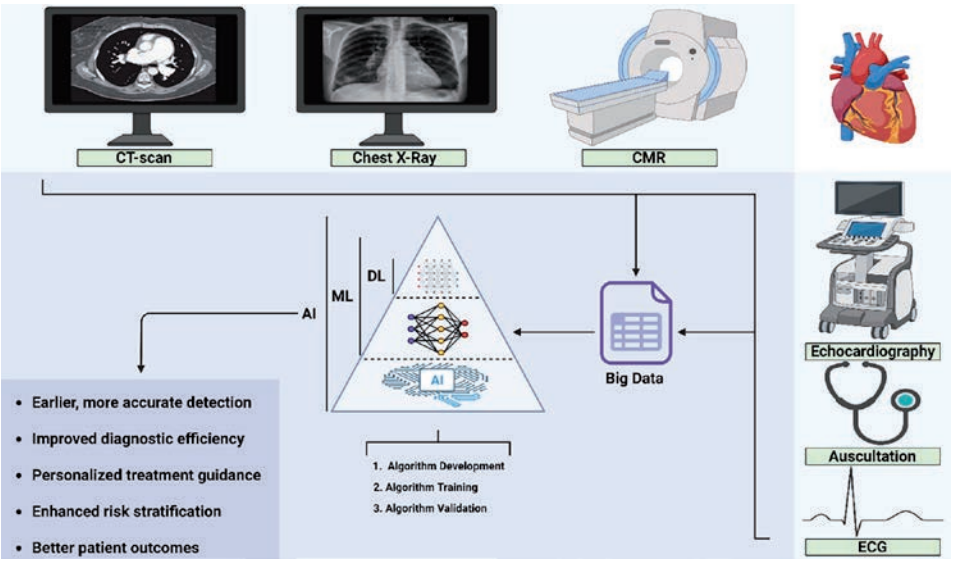


Figure 2.
This diagram represents the combination of multiple clinical data sources, such as cardiac auscultation, ECG, chest X-ray, echocardiography, CT, and CMR imaging, into massive information archives. This collection of data establishes a foundation for the construction, development, training, and validation of AI methods. The application of these AI models holds the potential to yield significant advancements in pulmonary hypertension management, including earlier and more accurate detection, improved diagnostic efficiency, personalized treatment guidance, enhanced risk stratification, and ultimately, better patient outcomes.

imaging, which form the foundation for developing and validating AI methods in PH. The figure highlights how combining these diverse data modalities enables earlier detection, improved diagnostic accuracy, risk stratification, and personalized management.

2.1 Heart auscultation

Auscultation remains a fundamental tool in medical evaluations and can aid in detecting PH, but even experienced clinicians may occasionally make diagnostic errors. This challenge is especially significant in low-resource settings, highlighting the need for reliable algorithmic support. Analyzing the acoustic characteristics of heart sounds presents a promising non-invasive approach to estimate pulmonary artery pressure and uncover underlying hemodynamic changes [10].

The detection of PH along with five additional cardiac conditions could be automated according to a different study. Wang et al. applied pretrained deep learning models using transfer learning techniques to phonocardiogram (PCG) data. The models included GoogleNet, SqueezeNet, DarkNet19, MobileNetv2, Inception-ResNetv2, DenseNet201, Inceptionv3, ResNet101, NasNet-Large, and Xception. These models were used to classify various cardiac conditions. Several models—such as ResNet101, DenseNet201, DarkNet19, and GoogleNet—achieved high PH-specific accuracy levels ranging from 0.90 to 0.98. Notably, these AI-powered techniques maintained strong predictive performance even in noisy environments, suggesting that the proposed classification method could be valuable for assisting in the detection of cardiovascular diseases [11].

2.2 Electrocardiography (ECG)

Given the limitations of current tools for early detection in at-risk patients and for effective monitoring in those with established PH, researchers have turned to AI-driven ECG analysis for prediction. Kwon et al. created a neural network system that uses 12-lead ECG waveforms (S-, P-, and T-waves) and demographic data. Trained on 56,670 ECGs from 24,202 individuals, the model achieved impressive performance with an AUC of 0.859 in internal and 0.902 in external validation. In individuals without baseline PH, the AI accurately stratified risk, identifying a 31.5% likelihood of PH development in the group at greater risk and 5.9% in the group with a low risk [12].

Early detection and treatment are crucial to mitigating the harmful effects of PH. Transthoracic echocardiography (TTE), which estimates maximum tricuspid regurgitation velocity, is the preferred non-invasive method for assessing pulmonary artery pressure. However, accurate measurements require high-quality imaging and expert technicians. Delays of up to 2 years between the onset of symptoms and the confirmation of ePAP can be observed [13]. In order to identify ePAP and forecast individuals' potential for cardiovascular death, Liu et al. created an AI-powered ECG algorithm using data from 41,097 individuals [14]. Their AI model had an AUC of 0.88 (sensitivity 81.0%; specificity 79.6%), as demonstrated by tests of 10-fold cross-validation neural-network deep learning, for identifying ePAP. Additionally, those who were estimated to have ePAP by the AI algorithm had a separate correlation with greater death from cardiovascular disease (HR: 3.69) following a 6-year monitoring.

A CNN called the PH Early Detection Algorithm (PH-EDA) was created utilizing retrospective ECG voltage-time metrics, and individuals are categorized as possible for PH or not possible according to RHC or echocardiography. In analysis of nearly 125,000 individuals, DuBrock et al. discovered that the method they developed could identify PH at diagnosis, 6–18 months, or 5 years earlier. AUC for PH detection was 0.92 and 0.88, respectively, after validation testing in two populations (104,173 and 30,301 patients), while when considering the pre-emptive test samples (6–18 months prior), the corresponding values were 0.86 and 0.81. For as long as 5 years before identification, they found that AUC maintained between 0.79 and 0.73 [15].

When it comes to diagnosing cardiovascular disease, the 12-lead ECG is the gold standard because it is both cost-effective and readily available. Because the ECG produces structural and time-dependent characteristics of the electrical discharge from the heart [16]., it is helpful because it provides a lot of data which offers light on fundamental cardiac function. Additionally, ECG algorithms powered by AI have created advances in the industry for quick identification of PH and other cardiovascular issues. Kalmady et al. created an algorithm for the simultaneous prediction of 15 prevalent CV diagnoses with the help of 1,605,268 ECGs taken from 244,077 adult individuals who submitted to a minimum of one 12-leadECG. The identified conditions were according to the International Classification of Diseases, 10th revision (ICD-10) codes. They utilized ECG data in conjunction with ResNet-based DL and extreme gradient boosting (XGB). In this study, 97,631 individuals and their initial ECGs were employed and the DL models achieved an AUROC of 84.773 (84.768–84.779)%, an AUPRC of 38.091 (38.083–38.098), an F1 score of 9.424 (9.421–9.428), a specificity of 81.805 (81.804–81.806), and an accuracy of 81.656 (81.654–81.657)% for PHTN [17].

2.2.1 Chest X-ray

Patients receiving assessment for PH typically get a chest X-ray (CXR) as an initial test. In individuals assumed to have PH, the American College of Chest Physicians suggested taking a CXR to find characteristics indicative of PH detection [18]. A confirmed diagnosis of illness often results in inappropriate CXRs, although a typical CXR cannot rule out PH [19]. Cardiomegaly owing to enlargement of the right atrium (RA) and hypertrophy of the right ventricle (RV), as shown by decreased retrosternal volume, is one of the CXR observations that supports the diagnosis of PH [1]. the right side of the cardiovascular system is more prominent on the frontal projection; [2] the central pulmonary arteries enlargement; [3] the vessels in the peripheral regions are pruned or lost; and [4] there is no empty space on the lateral computed tomography (CXR) when the right ventricle is enlarged [20]. X-rays can also help determine the cause. In the diagnostic process for patients being evaluated for PH, including those with Chronic Thromboembolic PH (CTEPH) due to pulmonary embolism (PE), a chest X-ray can be useful for assessing the possibility of left-sided cardiac disease as well as evaluating pulmonary parenchymal conditions such as emphysema or interstitial lung disease [21].

By using AI on the CXR, Kusunose et al. were able to detect ePAP and classify patients' likelihood of hospitalization for cardiac failure associated with PH. After training on 900 individual CXRs, they created a CNN to detect individuals having high PAP (> 20 mmHg). The AUC measured by separate analysis of the algorithm for increased PAP recognition was considerably improved (0.71 compared to 0.60 also compared to 0.63, all $p < 0.05$) compared to the AUC measured by assessments of CXR images and experienced operators. Additionally, the likelihood of heart failure that was associated with PH was twice as high among those whose PH had been estimated by AI as in individuals whose PH had not been estimated by AI [22].

Zou et al. developed a DL method using chest radiographs to detect PH, achieving high accuracy (AUC up to 0.970) with models like Inception V3, outperforming human radiologists in classifying PH and predicting pulmonary artery systolic pressure (PASP) [23]. Similarly, Imai et al. created a DL system for PAH detection using CXRs, demonstrating superior performance (AUC 0.988) compared to clinicians [24]. Meanwhile, Kıvrak et al. engaged a transfer learning-based algorithm to classify different PH types from X-ray images, achieving 86.14% accuracy and an average AUC of 0.945, further validating DL's potential in non-invasive PH diagnosis [25]. These studies collectively highlight DL's effectiveness in automating PH detection and classification from imaging data.

2.2.2 Echocardiography

TTE is a widely used, non-invasive tool for diagnosing PH, offering additional value in risk stratification, prognosis estimation, and treatment monitoring. Beyond diagnosis, it assesses PH-induced remodeling of the left and right heart, providing critical insights into disease progression. Identifying echocardiographic markers of poor outcomes is especially valuable given PH's high mortality risk, aiding in effective patient management and ongoing monitoring [26]. Janda et al. found an 83% sensitivity (95% CI 73 to 90) as well as a 72% specificity (95% CI 53 to 85) for the identification of PH using echocardiographic techniques in a meta-analysis [27]. Patients with less-than-ideal acoustic windows might receive lower-quality images, and there is no certainty of reliable reproducibility; these are just two of the many drawbacks of this approach.

However, a major drawback of non-invasive PH detection using echocardiography is the fact that it typically gives us a rough estimate of PAP instead of a precise measurement of PAP, which serves as the defining characteristic of PH (i.e., mPAP >20 mmHg at rest). Recognizing that TTE cannot provide an accurate identification of PH, the echocardiographic assessment of the probability of PH is an important part of deciding whether or not to perform RHC on individuals thought to have the condition [26]. If AI can overcome certain drawbacks, echocardiography will be an even more effective and dependable instrument for identifying and assessing individuals likely to suffer from PH.

Automated standpoint recognition and cardiac chamber segmentation were among the many functions that Zhang et al. trained and assessed as CNN models for PAH detection. That way, they could measure the sizes of the chambers and the total weight of the left ventricle, find out what the EF was, and make it easier to automatically calculate the longitudinal strain using speckle tracking. Having C statistics of 0.85, respectively, their developed CNN were able to identify PAH [28].

ML algorithms have the potential to autonomously evaluate the likelihood of PH by extracting characteristics obtained from conventional echocardiography. Liao et al. created an ML algorithm capable of automatically assessing the likelihood of PH using data from 346 individuals' parasternal short axis-papillary muscle level (PSAX-PML) views. The ML algorithm's performance in PH diagnosis remained considerably strong even after external validation with an AUC of 0.950 (95% CI: 0.897–1.000). These results showed that ML techniques functioned better than conventional echocardiography evaluations with an AUC of 0.945 compared with 0.892 ($p = 0.027$) [29].

Anand et al. developed an ML model using echocardiographic data from 7853 individuals to diagnose PH, attaining an AUC of 0.83 and 82% accuracy, 88% sensitivity, and 89% positive predictive value (PPV). Their approach demonstrated that ML could predict PH even without relying on tricuspid regurgitation velocity [30]. Similarly, Hirata et al. used ML to classify 885 patients into non-PH, precapillary PH, and postcapillary PH groups, employing 24 variables and logistic regression with elastic net regularization. The system they used obtained AUCs of 0.789, 0.766, and 0.742 for the respective categories, outperforming guideline-based echocardiographic assessments (59.4% vs. 51.6% accuracy, $p < 0.01$) and showing comparable performance in validation (59.4% vs. 57.8%, $p = 0.638$), suggesting its utility in PH classification [31].

Li et al. developed an ML-based automated tool using 3D echocardiography (3DE) to examine RV performance in 151 TEPH individuals, identifying RV ejection fraction (RVEF) as a marker of unfortunate results (hazard ratio 1.576, $p = 0.030$) [32]. Meanwhile, Murayama et al. created a DL algorithm to compute RVEF from 2D echocardiograms in 85 precapillary PH patients, achieving a mean absolute error of 7.67% compared to cardiac MRI. Their DL model outperformed traditional measures like tricuspid annular plane systolic excursion (TAPSE) in detecting severe (AUC 0.84 vs. 0.72) and mild (AUC 0.87 vs. 0.69) RV dysfunction, matching RV fractional area change (FAC) performance (AUC 0.90) [33]. These studies highlight ML/DL's potential in enhancing PH prognosis and RV function assessment.

2.2.3 Computed tomography (CT)

CT has a vital role in diagnosing and managing suspected or confirmed PH. Key CT findings in PAH include central pulmonary artery enlargement, Sudden tightening of peripheral vessels, RV remodeling, enlarged right heart chambers and bronchial arteries, and heterogeneous lung perfusion patterns indicative of vascular distortion [34]. In addition to helping with diagnosis, CT can also help with finding

the root of PH and distinguishing among numerous kinds of PH. Adults who are likely to have acute PE often undergo computed tomography pulmonary angiography (CTPA) imaging, which can also aid in the diagnosis of possible CTEPH [35]. Though conventional CT analysis in PH is often semi-qualitative and subjective, quantitative CT (QCT) offers numerical insights into pulmonary artery size and right ventricular function changes post-treatment. Advanced QCT integrates ML and DL to enhance early detection, characterization, risk assessment, and therapy monitoring. To overcome the impracticality of manually analyzing pulmonary vessels in large-scale settings, Nardelli et al. developed an automated method combining scale-space particle segmentation, a 3D CNN, and graph-cut optimization to distinguish arteries from veins in chest CT images. This approach outperformed traditional classifiers and CNN variants, achieving a 94% accuracy rate [36].

The combination of echocardiographic pressure assessments and automated 3D volumetry of the major pulmonary arteries according to CTPA results in a more accurate non-invasive prediction of mPAP and PH than either method would provide on its own. By applying CTPA and TTE to diagnose possible cases of PH, Melzig et al. evaluated 70 individuals. They discovered that out of numerous metrics, the size of the main pulmonary arteries (MPA) exhibited the highest association with invasive mPAP ($r = 0.76$, $p < 0.001$) through the use of a regression model. Additionally, they discovered that invasive mPAP was highly correlated with estimated mPAP when they used MPA volume and echocardiographic pulmonary arterial systolic pressure (PASP) as covariates ($r = 0.89$, $p < 0.001$) [37].

In order to accurately differentiate between PH individuals who have mPAP and sPAP, Zhang et al. created a completely automated system for PAP evaluation. The system allows for precise pulmonary artery and heart segmentation. The mean segmentation dice score went up from 87.3% ± 2.9 to 88.2% ± 2.9 after they automated the extraction of structural characteristics of the pulmonary artery and heart on CTPA individuals using an ML algorithm. This was achieved by segmenting eight structural components of the pulmonary artery and heart using a segmentation system. The PAP variables were also predicted using a regression model, and patients were categorized using mPAP and sPAP using a classification model. There is a strong relationship among mPAP, left atrial size ($r = 0.333$, $p = 0.012$), left ventricle size ($r = -0.400$, $p = 0.002$), left atrium area ($r = -0.208$, $p = 0.123$), and pulmonary artery pressure ($r = -0.470$, $p = 0.000$) according to the associations among PAP and CTPA characteristics. The AUC for the mPAP classification system was 0.911, while for the sPAP classifier it was 0.833. An ICC of 0.934 was additionally determined for mPAP in the regression model, while 0.903 occurred for sPAP and 0.981 was found for dPAP [38].

Classification of risks without invasive procedures is possible with the application of ML on imaging information. A supervised ML approach has been constructed to forecast hemodynamic risk factors in 127 individuals based on an evaluation of 19 qualitative/quantitative image characteristics and 3 hemodynamic variables: mean MAP, RAP, and pulmonary artery oxygen saturation (PA SaO_2). Researchers applied a random forest algorithm to predict PH risk categories, achieving AUC scores of 0.82 and 0.74 for models based on mPAP and PA SaO_2, respectively. Key predictive features included mosaic attenuation, the right atrium-to-left ventricle ratio, and contrast retention in the hepatic vein, highlighting critical imaging biomarkers for PH risk stratification [39].

Another indicator of prognosis for individuals with non-operative CTEPH is the right-to-left ventricle diameter ratio (dRV/dLV) on CTPA. In order to calculate dRV/dLV, Shikhare et al. developed a new ML method. The investigators discovered

that dRV/dLV had an association with an increased risk of CTEPH and was also individually linked to a longer time spent in the intensive care unit (OR = 3.79, 95% CI 1.1–13.06, p = 0.035). Additionally, there had been a modest association between dRV/dLV and RV expansion on echocardiography and measurements of PH on RHC (r = 0.5–0.6, p < 0.0001) [40].

2.2.4 MRI

CMR acts as a powerful, safe instrument for determining, monitoring, and managing PH. It enables assessment of therapy effects over time, differentiates PH subtypes through markers like interventricular septal angle, and measures pulmonary arterial stiffness. While CMR yields rich physiological insights, interpretation can be time-consuming and expertise-dependent. However, research indicates that AI can enhance the efficiency and accuracy of PH evaluation using CMR data.

2.2.4.1 Automated segmentation and feature extraction

To address issues like image defects and complicated instances like PH, an investigation presented a DL-based procedure for completely automated 3D biventricular segmentation of CMR data [41]. To ensure consistent and clinically relevant results, a segmentation pipeline integrated shape refinement *via* morphological priors with a multi-task network for landmark detection and segmentation. Utilizing a 2.5D model preserved 3D spatial consistency while maintaining computational efficiency. Validated on 1831 high-quality volumes, the pipeline achieved high segmentation accuracy, with dice scores of 0.946 ± 0.026 for the LV cavity and 0.912 ± 0.041 for the RV cavity. On 600 simulated not high-quality volumes, the pipeline achieved 0.926 ± 0.031 for the LV and 0.892 ± 0.046 for the RV. The RV wall obtained considerably lower precision compared to the pipeline, which obtained good general accuracy. Twenty individuals from the PH subset were used to instruct and assess the framework on abnormal not high-quality volumes. Visuals with aberrant RV dilatation and displacement were successfully segmented, allowing for the measurement of RV anatomy and function. Manually segmenting of the related images with excellent resolution yielded a volume of 148.73 ± 54.23 mL, while the model estimated the RV cavity volume as 146.69 ± 52.96 mL.

In order to enhance the evaluation of PH, Ma et al. [42] used a DL-based method combining CNN with the You Only Look Once (YOLO) method, enabling automatic and highly accurate RV segmentation in cardiac MRI, obtaining a dice coefficient of 0.89 and 99.4% accuracy, outperforming common methods such as active shape models and random forests. The AI system effectively identified key PH-related features, such as pulmonary artery dilatation and RV wall hypertrophy, offering a comprehensive, non-invasive alternative to echocardiography for RV assessment without the need for additional imaging.

2.2.4.2 Diagnosis and differentiation of PH

Applying imaging parameters and mathematical models obtained from MRI, Lungu et al. [43] used ML to improve non-invasive PH detection. A total of 72 individuals who were able to undergo each RHC and CMR were enrolled in the investigation. The ML approach generated a 92% diagnosis precision (sensitivity: 97%; specificity: 73%), by combining biochemical measures like PVR, compliance, and

wave reflection ratio (Wb/Wtot, ratio of backward to total wave power) to structural characteristics like RV ejection fraction, ventricular mass index, and systolic septal angle. By combining these measures gathered from images and computing, the diagnostic accuracy was greatly enhanced, with an AUC of 0.91 compared to 0.89 for each of the measures. While changes in pulmonary artery area offered additional clinical insights, the wave reflection ratio acted as the best independent marker for PH. This investigation emphasizes the possibilities for merging sophisticated imaging with algorithmic analysis to lessen dependency on invasive diagnostic methods like RHC.

To diagnose PAH, researchers in a further investigation used a tensor-based ML method with CMR images [44]. This approach eliminated the need for manual segmentation by reducing high-dimensional CMR information to understandable diagnostic characteristics using multilinear subspace learning.

2.2.4.3 Prognostic assessment and risk stratification

By examining 3D RV motion patterns obtained from CMR, a supervised ML algorithm was created to forecast the probability of survival for individuals with PH [45]. Using ML, the researchers were able to identify important motion predictors of undesirable results, including decreased basal longitudinal motion and transverse contraction in the septum and RV free wall, in a trial that encompassed 256 people who were recently diagnosed with PH. The average lifespan for high-risk and low-risk groups was significantly different (13.8 vs. 10.7 years, $p < 0.001$), and the AUC enhanced from 0.60 to 0.73 ($p < 0.001$) when 3D motion was incorporated into lifespan predictions. Automated RA area measuring with CMR in PH individuals was created and confirmed by Alandejani et al. [46]. The algorithm outperformed manual measures in terms of repeatability (ICC 0.91–0.95) when developed on a multicenter sample of 365 patients. The RA area measures produced by AI remained accurate and showed slight correlations with invasive hemodynamics in a medical study group of 400 individuals ($r = 0.64$ for mean RAP). The AI algorithm was also able to accurately forecast the median RAP risk levels set by the European Society of Cardiology and the European Respiratory Society (ESC/ERS), with AUCs varying from 0.82 to 0.90. In addition, the HR for death was 1.02 ($p < 0.01$), whether the RA area estimates were taken manually or by AI. Employing a multicenter collection with various cardiovascular diseases, particularly PH, a different DL algorithm for automatic CMR evaluation was created and verified [47]. In comparison to human evaluations, the algorithm showed a significant correlation with RHC values including mPAP ($r = 0.56$) and PVR ($r = 0.62$). Results from a predictive evaluation of 3487 individuals suffering from PH demonstrated that RV measures, such as RVEF (HR 0.80, $p < 0.001$), RV end-diastolic volume, and ventricular mass index, are useful in forecasting death in PH. Reducing variability in RV evaluations is possible thanks to the algorithm's good interstudy consistency (ICC > 0.90) and applicability throughout various vendors and sites. To predict 1-year mortality in treatment-naïve PAH individuals, a further investigation used an ML model that utilized multilinear principal component analysis (MPCA) to gather predictive characteristics from CMR [48].

3. Pulmonary hypertension treatments

PH management aims to relieve symptoms, boost exercise capacity, and improve survival. Initial treatments often include oxygen for hypoxemia, diuretics for fluid

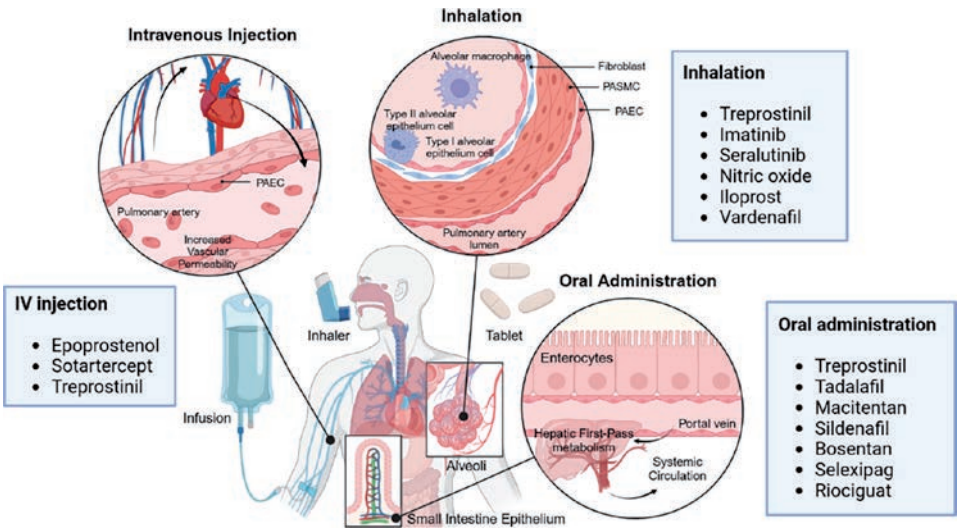


Figure 3.
The multifaceted landscape of pulmonary therapeutics necessitates a diverse arsenal of delivery methodologies. As visually represented, the administration of pharmacological agents to the respiratory system is achieved through several key pathways: nebulization, which transforms liquid formulations into inhalable aerosols; the inhalation of micronized powders via *Dry Powder Inhalers (DPIs); and the precise dispensing of medication through Metered Dose Inhalers (MDIs). Reproduced from Park et al. [49] under the terms of the Creative* Commons Attribution License (CC BY).

control, and anticoagulants for specific types like CTEPH. Lifestyle changes, including pulmonary rehabilitation and avoiding symptom-triggering activities, further support patient well-being.

Pharmacological treatment is central to managing PH, targeting multiple pathways involved in its development. Key drug classes involve pulmonary vasodilators—such as phosphodiesterase-5 inhibitors, endothelin receptor antagonists, soluble guanylate cyclase stimulators, and prostacyclin analogs, that work to relax and widen pulmonary arteries. Medication choices depend on the individual's WHO functioning category, underlying cause of PH, and treatment response. In advanced cases, combination therapy using multiple drug classes and diverse delivery methodologies is often employed to achieve better hemodynamic and clinical outcomes (**Figure 3**) [50].

4. Personalized treatment strategies through artificial intelligence

PH represents a complex disease spectrum characterized by considerable phenotypic heterogeneity and widely variable responses to existing therapies. A significant challenge stems from the fact that PH often presents as a convergent phenotype, the late-stage manifestation of multiple underlying pathological drivers, making it difficult to dissect using blunt clinical descriptors alone [51]. Patient responses to drugs in PH are highly variable, a nuance often lost when results are averaged across groups. This underscores the shortcomings of generalized treatment strategies and advocates for personalized medicine. Future PH therapies should prioritize individual patient characteristics, which requires a revised classification of pulmonary vascular diseases that incorporates detailed clinical and molecular data to identify treatable patient subgroups [52].

The advancement toward personalized medicine in PH is increasingly reliant on the capacity to analyze extensive and diverse patient data sets, often referred to as 'big

data'. Progress in understanding PH pathogenesis hinges on integrated approaches that combine electronic health records, advanced imaging, and molecular-omics profiling. This comprehensive strategy, known as 'deep phenotyping,' gathers detailed clinical, genetic, and molecular data, such as transcriptomics, proteomics, metabolomics, and microbiomics, enabling a nuanced and individualized understanding of disease mechanisms [53]. Advanced technologies like next-generation sequencing have uncovered rare and common genetic variants that contribute significantly to idiopathic pulmonary arterial hypertension (IPAH). Complementary molecular tools, transcriptomics, proteomics, and metabolomics, reveal dynamic molecular patterns linked to PH's onset, severity, and prognosis. In parallel, high-resolution imaging, especially cardiac MRI, delivers detailed, high-dimensional data that capture nuanced cardiac phenotypes often missed by conventional metrics [54]. Integrating these data streams, including information from wearable sensors and electronic health records, creates detailed databases amenable to advanced analysis.

AI, particularly ML, offers robust tools for interpreting complex, high-dimensional datasets like those from omics and imaging studies in PH. Unlike traditional statistics, ML excels at modeling intricate, non-linear relationships and managing large variable sets. Supervised ML, trained on labeled data, can predict outcomes such as disease status or treatment response. These models have already demonstrated utility in PH, accurately distinguishing PH subtypes *via* cardiac MRI and predicting IPAH risk from electronic health record patterns, enabling earlier diagnosis and intervention [55, 56].

Crucially for personalized therapy, ML can help identify predictors of treatment response. By analyzing molecular data (like cytokines, chemokines, or other biomarkers) from clinical trials, supervised ML algorithms can uncover baseline 'responder signatures' predicting which individuals are most probable to gain advantages *via* a particular treatment. Such responder profiles could be invaluable for enriching future clinical trial cohorts, improving study power and efficiency, especially in a rare disease like PAH [57]. The ultimate goal is to leverage these AI-driven insights to select the optimal therapeutic strategy for each individual patient, improving outcomes in this challenging disease.

5. Conclusion

The combination of AI into PH investigation and clinical care has shown significant promise across multiple diagnostic modalities. Our chapter underscores the performance of AI-based models in enhancing early detection, risk stratification, and individualized patient management. Notably, CNNs and transfer learning models have demonstrated high accuracy (AUCs up to 0.98) in classifying PH from phonocardiograms, ECGs, and chest radiographs. Echocardiography-based algorithms, particularly those leveraging 3D or ResNet-enhanced frameworks, have shown strong predictive capacity even without traditional velocity markers. Imaging-based models using CT and CMR have facilitated non-invasive estimation of PAP and RV activity, correlating strongly with invasive measures. Moreover, AI-driven tools have improved mortality prediction by analyzing complex 3D cardiac motion and radiomic features. These advancements allow for earlier diagnosis, better phenotyping, and dynamic risk stratification. In addition, machine learning algorithms have begun to personalize therapy by predicting patient-specific treatment responses using integrated omics and imaging data. Overall, AI holds transformative potential in the PH care continuum, addressing current diagnostic limitations and paving the way for precision medicine (**Table 3**).

AI-developed method	Study	Study population (training and validation)	Diagnostic tool	Key findings	Limitations
auscultation	[58]	60 individuals, comprising 25 with PAH and 35 without PAH	RHC	The method demonstrated a sensitivity of 84% and a specificity of 88.57% for PAH versus non-PAH categorization, utilizing cardiac sounds captured in the second left intercostal area.	• Restricted applicability
auscultation	[59]	An algorithm was applied to a group of 373 individuals identified as having CHD-PAH. The investigation lacked particular information regarding the training and verification methods used to confirm the identification of CHD-PAH.	Echocardiography (Further investigation was not conducted for anybody).	In a group of 88 persons, comprising 44 confirmed cases of CHD-PAH and 44 controls, the RNN demonstrated 90% success rate for accurately classifying those involved as either positive or negative for CHD-PAH.	• Restricted capacity for generalization. • Insufficient data exists concerning the CHD-PAH category. • Absence of verifying echocardiography for all examined people may result in the mistake for certain cases.
ECG	[60]	5016 individuals with PH and 19,454 non-PH. A total of 172 individuals were allocated at random to one of three groups: training, development, or testing.	RHC or TTE	The AUC for PH detection was 0.89, with a sensitivity of 0.79 and a specificity of 0.84. The different types were identified having AUCs $\geq$0.79 for a maximum of 2 years before identification.	PH is not always confirmed through the RHC across all instances. There may been a mistake regarding the individuals' PH subgroup classifications. Inadequate external verification.

AI-developed method	Study	Study population (training and validation)	Diagnostic tool	Key findings	Limitations
ECG	[61]	They randomly allocated 85,193 individuals who had ECG or CXR with TTE to one of three groups: model creation (n = 42,299), tuning (n = 17,182), or internal validation (n = 25,512) at Hospital A. For the external validation set, Hospital B used 16,736 patients who had an ECG, CXR, or TTE.	PASP exceeds 50 mmHg as determined by TTE.	• AUCs for ePAP prediction: • Combinational internal validation: 0.8644, ECG: 0.8525, and CXR: 0.8261. • Combo of ECG and CXR yields independent verification of 0.8348, 0.8605, and 0.8734, respectively. • A There was a broad spectrum of sensitivity and specificity (71–86%), NPV (97–99%), and PPV (18–24%). • Risk of dysfunction of the left ventricle in coming years was prediCted using a combined ECG and CXR model at 4.51 (95% CI: 3.54–5.76) and 6.08 (4.66–7.95), as well.	• PH is not always confirmed through the RHC across all instances. • Inadequate external verification.
CXR	[62]	52 individuals who had EIPH determined by 6-MW stress echocardiography conducted exercise RHC out of 142 patients at-risk for PAH (SSc or MCTD with SSc characteristics) who had actual TTE results.	Exercise RHC.	The AI algorithm had an AUC of 0.71 (95% CI: 0.62–0.78). The AI approach enhanced the fundamental framework by include the chance of PH estimated by the method. The fundamental framework already included age, sex, blood pressure, and mean PAP at resting with an AUC ranging from 0.65 to 0.74; p-value = 0.046.	• PH is not always confirmed through the exercise RHC across all instances. • There is a lack of generalizability due to an insufficient man population sample and the possibility of cohort bias.
CXR	[63]	There were 1174 CHD images and 2081 non-CHD images. -To evaluate physicians and AI algorithms, along with physicians having and not having AI support, a sample of 165 CHD pictures were randomly chosen, with 19 (11.52% of the total) being PAH-CHD. The remaining 165 images were not CHD.	echocardiography.	Utilized ImageNet pretrained variables for transfer learning. The AI algorithm outperformed physicians in identifying CHD and PAH-CHD from CXRs, having AUCs that were greater. With the use of AI, physicians were able to dramatically enhance the accuracy of diagnosis of PAH-CHD (AUC raised from 0.639 to 0.705, $p < 0.05$).	• PAH is not always confirmed through the RHC across all instances.

AI-developed method	Study	Study population (training and validation)	Diagnostic tool	Key findings	Limitations
CXR	[25]	of 2145 individuals, 4497 CXRs were performed. 2145 CXRs were used as the control sample in this study.	Echocardiography.	The top-performing model attained an accurate classification rate of 86.14% in six different groups (five PH kinds and non-PH), which is much better than the visual evaluation and categorization according to published recommendations performed by 4 specialists who had no access to patients' medical histories. It was able to differentiate among PH and non-PH cases with an AUC of 0.945.	Some groups of the dataset are imbalanced. Its applicability is restricted.
Echocardiography	[64]	There were a total of 936 TTE films of 192 infants in the training and validation collection, and a further 375 TTE recordings of 78 newborns in the held-out test set.	A cardiologist visual evaluation	The spatio-temporal multi-view DLM was able to identify binary PH with an F1-score of 0.92 and forecast intensity with an F1-score of 0.84.	Restricted applicability. TTE is used for PH identification and intensity evaluation.
Echocardiography	[65]	116 cases for derivation and 142 cases for validation from outside sources.	RHC.	A strong connection between predicted mPAP and RHC (R = 0.96) was found; a mPAP greater than 29.9 mmHg was associated with higher likelihood of 2-year mortality.	Some metrics are vulnerable to changes in heart and volume status during measurement; –there is not enough outside verification.
Echocardiography	[33]	85 patients (compositing 73 PH individuals).	-RHC -CHEST MRI.	Considering a mean absolute error of 7.67%, the RVEF was properly predicted. -Similar AUC of RV failure to a specialist sonographers.	It is possible that some settings were altered between evaluations.
CT	[66]	300 samples from two groups: In the first cohort, there were 8 control subjects, 80 cases of lung illnesses other than CTEPH, and 80 cases of CTEPH itself. Within the second cohort, there were 124 individuals who served as healthy controls.	*via* clinical and imaging criteria.	In comparison with NCCT techniques lacking the use of AI (AUC:0.760) and techniques utilizing V/Q scans (AUC:0.670), the algorithm's accuracy for CTEPH diagnosis was improved (AUC: 0.807).	Restricted applicability. Data is not balanced.

AI-developed method	Study	Study population (training and validation)	Diagnostic tool	Key findings	Limitations
CT	[67]	Training and testing of 127 preoperative CTEPH individuals were conducted using a threefold random sample.	RHC.	AUC of 0.82 was achieved for mPAP forecasting, highlighting significant characteristics such as the RV/LV ratio and mosaic attenuation sequences.	Absence of external validation. Manual choice of characteristics. Data are not balanced.
CT	[68]	There was a training cohort of 275 people and a test cohort of 246 people.	*Via* clinical and imaging criteria.	There was an independent association between AI-quantified fibrosis and greater death rates (HR: 1.01, $p = 0.04$), but when paired with radiologic grading, it enhanced the survival prognosis (C-index: 0.67 vs. 0.61, $p < 0.001$).	Data are not balanced. Restricted applicability.
CT	[69]	99 operated CTEPH cases.	*Via* imaging and clinical data.	The RV/LV ratio was associated with the degree of illness and by itself forecasted an extended duration of stay in the ICU following operation (OR = 3.79, 95% CI 1.1–13.06, $p = 0.035$).	They did not use an internal cohort to train the pretrained model. No independent verification. In severe cases, the ML tool did not work.
CHEST MRI	[70]	Out of 312 people with PH, 182 had metabolic testing done. Also there were 1985 healthy participants.	Not specified.	A distinct indicator of mortality in PH individuals was RV wall stress, as measured using AI-assisted biomechanical modeling (hazard ratio 1.27, $p = 0.04$), according to the model.	Absence of external validation. Diverse patient population. Duration within assessments.
CHEST MRI	[71]	Training and test sets were created using 42 PH individuals as well as 30 controls, respectively.	RHC.	Among the models that used CHEST MRI textural features to distinguish PH individuals from controls, the MLP model performed the finest with an AUC of 0.862 and an accuracy rate of 78%.	Absence of external validation. Concentrated solely on LV texture characteristics.
CHEST MRI	[56]	42 PH, 40 healthy individuals.	RHC.	Radiomics-based ML utilizing CHEST MRI with the DAFIT approach successfully distinguished PH patients of healthys with a good diagnosis accuracy (AUC: 0.958).	Limited number of samples. Absence of external validation. Practical intricacy.

AI-developed method	Study	Study population (training and validation)	Diagnostic tool	Key findings	Limitations
CHEST MRI	[72]	The primary dataset contains 1250 observations, 134 PAH, and 6516 other cardiovascular diseases; the external test dataset contains 403 controls, 66 PAH, and 1350 other CVDs.	RHC.	Outperforming professional cardiologists and displaying robust external validation across several sites, an AI-enabled CHEST MRI strategy was able to achieve 99.8 percent AUC in determining PAH through integrating cine and late gadolinium enhancement techniques.	Unbalanced dataset.
CHEST MRI	[45]	256 PH patients.	RHC.	The design employs three-dimensional RV motion structures from CHEST MRI Enhanced likelihood of survival in PH individuals, with an increase in the AUC coming from 0.60 toward 0.73 ($p < 0.001$).	Lack of external validation. Restricted applicability.

Table 3.
Overview of AI-based tools applied in PH detection and diagnosis, highlighting their diagnostic modalities, key findings, and performance outcomes compared to conventional methods.

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Edited by Kian Chung Ong

Chronic Obstructive Pulmonary Disease (COPD) is a common and complex disorder that requires frequent updates of one's knowledge base. The annual updates to the guidelines for the management of COPD, issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) since its inception at the turn of the century, are a testament to the need for ongoing, informed updates in confronting the disease. Likewise, this editor and publisher have produced a succession of books on COPD since the first volume in 2012. In its latest iteration, preserving its open-access and peer-reviewed format, the present book combines the knowledge and experience of professionals from diverse backgrounds worldwide, presenting scientific information in an academic format that aims to contribute to the extensive and progressive research and practice in COPD.

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