REVIEW ARTICLE

PHYSIOPATHOLOGICAL MECHANISMS OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE DISEASES

Anxhela Qirko (Gurakuqi) [1], Taulant Gishto [2]
[1]Head of the Department of Physiopathology, Faculty of Medicine, UMT, Tirana
Allergy Specialist, Service of Allergology and Clinical Immunology, UHC, Tirana
[2]Lecturer at the Department of Physiopathology, Faculty of Medicine, UMT, Tirana
Cardiology Specialist, Service of Cardiology, UHC, Tirana
Corresponding E-mail: anxhela_g@yahoo.com

ABSTRACT

This article summarizes the main pathophysiological mechanisms that link chronic obstructive pulmonary diseases, especially COPD and emphysema, to the development of pulmonary hypertension (PH). Unlike bronchial asthma, COPD and emphysema are characterized by irreversible obstruction, mainly associated with structural changes in the bronchial wall and destruction of the alveolar architecture, mainly caused by smoking. In COPD, mucus hyperproduction, hypertrophy of mucous glands, and decreased mucociliary clearance follow persistent airway narrowing, while in emphysema, damage to elastic fibers due to protease–antiprotease imbalance predominates, resulting in bronchiolar collapse and "air trapping".

These structural changes also progressively affect the pulmonary vascular bed, leading to the installation of PH through several interconnected mechanisms. Alveolar hypoxia causes hypoxic vasoconstriction, a compensatory mechanism that diverts blood flow to more ventilated areas, but which chronically increases vascular resistance. Chronic inflammation induced by smoking favors a profile of vasoconstrictor mediators and impairs endothelial function. Vascular remodeling, mediated by factors such as TGF-β, contributes to vascular wall stiffening and thickening, making the process irreversible.

Other factors include polycythemia in response to hypoxia, vasoconstrictive acidosis, pulmonary thromboses that worsen the ventilation/perfusion ratio, and the reduction of the capillary network in emphysema, which reduces the surface area for gas exchange. Pulmonary hyperinflation and increased intrathoracic pressures negatively affect venous return and cardiac output, activating the sympathetic system and the renin–angiotensin–aldosterone system, which further potentiate pulmonary vasoconstriction.

In **conclusion**, PH in the context of COPD and emphysema is the result of a complex interaction between hypoxia, inflammation, vascular remodeling, and hemodynamic factors, representing an important prognostic and therapeutic complication.

Key words: Chronic obstructive diseases, COPD, emphysema, pulmonary hypertension, PH

MEKANIZMAT FIZIOPATOLOGJIKË TË HIPERTENSIONIT PULMONAR, NË PACIENTË ME PATOLOGJI OBSTRUKTIVE KRONIKE

ABSTRAKT

Ky artikull përmbledh mekanizmat kryesorë fiziopatologjikë që lidhin patologjitë obstruktive kronike pulmonare, veçanërisht SPOK-un dhe emfizemën, me zhvillimin e hipertensionit pulmonar (HTP). Ndryshe nga astma bronkiale, SPOK-u dhe emfizema karakterizohen nga obstruksion jo i kthyeshëm, i lidhur kryesisht me ndryshime strukturore të murit bronkial dhe shkatërrimin e arkitekturës alveolare, të shkaktuara kryesisht nga duhani. Në SPOK, hiperprodhimi i mukusit, hipertrofia e gjëndrave mukoze dhe ulja e klirensit mukociliar çojnë në ngushtim të qëndrueshëm të rrugëve ajrore, ndërsa në emfizemë dominon dëmtimi i fibrave elastike për shkak të çekuilibrit proteazë–antiproteazë, me pasojë kolaps bronkiolar dhe "air trapping".

Këto ndryshime strukturore ndikojnë progresivisht edhe në shtratin vaskular pulmonar, duke çuar në instalimin e HTP përmes disa mekanizmave të ndërthurur. Hipoksia alveolare shkakton vazokonstriksion hipoksik, një mekanizëm kompensator që devijon rrjedhën e gjakut drejt zonave më të ventiluara, por që në mënyrë kronike rrit rezistencën vaskulare. Inflamacioni kronik i nxitur nga duhani favorizon një profil mediatorësh vazokonstriktorë dhe dëmton funksionin endotelial. Rimodelimi vaskular, i ndërmjetësuar nga faktorë si TGF-β, kontribuon në ngurtësimin dhe trashjen e murit vaskular, duke e bërë procesin të parikthyeshëm.

Faktorë të tjerë përfshijnë policiteminë si përgjigje ndaj hipoksisë, acidozën me efekt vazokonstriktor, trombozat pulmonare që përkeqësojnë raportin ventilim/perfuzion, si dhe reduktimin e rrjetit kapilar në emfizemë, që ul sipërfaqen e shkëmbimit të gazeve. Hiperinflacioni pulmonar dhe rritja e presioneve intratorakale ndikojnë negativisht në kthimin venoz dhe debitin kardiak, duke aktivizuar sistemin simpatik dhe sistemin reninë–angiotenzinë–aldosteron, të cilët përforcojnë më tej vazokonstriksionin pulmonar.

Në përfundim, HTP në kontekstin e SPOK dhe emfizemës është rezultat i një ndërveprimi kompleks midis hipoksisë, inflamacionit, rimodelimit vaskular dhe faktorëve hemodinamikë, duke përfaqësuar një komplikacion të rëndësishëm prognostik dhe terapeutik.

Fjalë kyçe: Sëmundje obstructive kronike, SPOK, emfizemë, hypertension pulmonar, HTP

INTRODUCTION

Chronic obstructive pulmonary diseases, including bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), and emphysema, represent a major challenge for global public health. These conditions are characterized not only by structural and functional changes in the bronchial tree - such as increased airway resistance - but also by a progressive and often irreversible damage to the pulmonary vascular bed. While in bronchial asthma, vascular changes may be more limited and often associated with TH2-type inflammation, in COPD and emphysema, vascular alterations predominate over the course of the disease (1).

The statistics are alarming: by 2030, COPD is predicted to be the fourth leading cause of death globally. The main etiology remains smoking, which triggers a cascade of reactions ranging from mucus hyperproduction to parenchymal destruction. In COPD, the obstruction is largely irreversible due to bronchial wall thickening (Reid index increase above 0.7) and mucous gland hypertrophy. On the other hand, emphysema represents the most aggressive form of structural destruction, where the loss of peri-bronchial and peri-alveolar elastic fibers leads to the collapse of small airways and the formation of areas of "air trapping".
Pulmonary Hypertension (PH) in these patients is a serious complication that determines survival (2). According to the latest ECS/ERS 2022 guidelines, PH is diagnosed when the Mean Pulmonary Artery Pressure (mPAP), measured by cardiac catheterization, exceeds 20 mmHg. This transition from a purely respiratory disease to a condition with severe hemodynamic implications occurs through a series of complex pathophysiological mechanisms that will be analyzed below.

DETAILED ANALYSIS OF PATHOPHYSIOLOGICAL MECHANISMS

Below are listed and elaborated on 9 mechanisms that lead to the installation and progression of PTH in the setting of chronic obstruction:

1. Alveolar Hypoxia and Hypoxic Pulmonary Vasoconstriction (HPV): This is the earliest and most critical mechanism (3). The pulmonary vascular bed possesses a unique property: unlike the systemic circulation (where hypoxia induces vasodilation), in the lungs, it causes vasoconstriction of pre-capillary arterioles. This process is known as the Euler-Liljestrand Reflex. The physiological purpose is protective: to divert blood from poorly ventilated alveoli to those with high oxygen levels, attempting to maintain the ventilation/perfusion (V/Q) ratio and minimize the “shunt effect.” However, when hypoxia becomes chronic and widespread (as in COPD), this vasoconstriction becomes ubiquitous, dramatically increasing pulmonary vascular resistance and serving as a cornerstone for PH.

2. Chronic Inflammation and Humoral Mediators: Tobacco and other irritants induce a chronic inflammatory state in the airways and blood vessels (4). This inflammation is characterized by increased chemotaxis of neutrophils, which are the main source of elastase. At the endothelial level, this inflammation causes an imbalance between vasoactive substances. There is an increase in the production of Endothelin-1 (a potent vasoconstrictor) and the activity of the enzyme ACE, while the availability of protective vasodilator substances such as Nitric Oxide (NO) and Prostacyclin decreases. This biochemical imbalance keeps the blood vessels in a state of constant high tone.

3. Vascular Remodeling and the Role of TGF-β: If vasoconstriction is a functional phenomenon, remodeling is the structural transformation that makes HTP irreversible (5). Under the influence of growth factors such as PDGFA, PDGFB, and especially TGF-β (Transforming Growth Factor beta), endothelial remodeling and dysfunction occur, as well as proliferation of smooth muscle cells in the arteriolar wall, together with an excessive deposition of extracellular matrix. This process damages the endothelium and "muscularizes" the normally thin vessels. Today, scientific attention has focused on drugs such as

Sotatercept, which act as a "trap" for TGF-β, aiming to block this signaling and potentially reverse vascular remodeling. Endothelial dysfunction is also directly provoked by smoking itself

4. Secondary Polycythemia and Blood Viscosity: Because of chronic hypoxia, the kidneys stimulate the production of erythropoietin, which leads to an increase in the number of erythrocytes, provoking polycythemia (6). Although this is intended to increase the oxygen-carrying capacity, the hemodynamic consequence is an increase in blood viscosity. According to Poiseuille's law, increased viscosity directly increases resistance to flow, requiring more pressure from the right ventricle to move blood through the pulmonary circulation.

5. Action of Acidosis: In patients with COPD, the tendency for CO_2 to accumulate in the blood leads to acidosis from hypoventilation (7). Interestingly, the decrease in pH has a synergistic effect with hypoxia in promoting pulmonary vasoconstriction. Acidosis modifies ion channels in vascular smooth muscle cells, promoting calcium entry and contraction, which further increases the load on the pulmonary artery.

6. "In-situ" Thrombosis and Microembolism: The combination of endothelial damage with blood stasis due to increased viscosity creates a state of hypercoagulability (8). Local thrombi (in situ) can form in small pulmonary vessels. These thrombi not only physically block the blood circulation but also release mediators such as Thromboxane A2 (TXA2), an extremely potent vasoconstrictor, creating a vicious cycle of increased pulmonary arterial pressure (PAP). Another consequence of thrombosis is the further deterioration of the ventilation/perfusion (V/P) ratio. It is known that in the context of the underlying disease (COPD and emphysema), this ratio has almost always been abnormal.

7. Destruction of the Capillary Bed in Emphysema: This is a purely structural mechanism. The destruction of the alveolar walls in emphysema also brings with it the disappearance of the capillaries located in those walls (9). With the loss of the total surface area of the vascular bed, the same volume of blood must pass through fewer vessels, which automatically increases the perfusion pressure (similar to reducing the number of lanes on a highway).

8. Hyperinflation and Intrathoracic Pressure Changes: In emphysema, "air trapping" causes the lungs to be constantly inflated, in a state of hyperinflation. This increases the positive intrathoracic pressure, which impedes venous return to the heart (10). The subsequent decrease in cardiac output activates the sympathetic nervous system, which, through alpha-adrenergic receptors, promotes further pulmonary vascular vasoconstriction.

9. Activation of the Renin-Angiotensin-Aldosterone System (RAAS): When cardiac output falls due to high intrathoracic pressures and right ventricular failure, not only is the sympathetic system stimulated, but the RAAS also becomes active as a compensatory mechanism (11). Angiotensin II, the main product of this system, is, among other things, a potent vasoconstrictor that acts both in the systemic circulation and in the lungs. This activation of Angiotensin II accelerates the transformation of mild hypertension into a severe hemodynamic state.

DISCUSSION

The link between PH and Cor Pulmonale in contemporary literature

The link between Pulmonary Hypertension and Cor Pulmonale represents one of the most sensitive points of modern cardiology and pneumology. Cor Pulmonale is defined as hypertrophy and dilatation of the right ventricle (RV), as a consequence of lung diseases that cause PH (Fig.1).

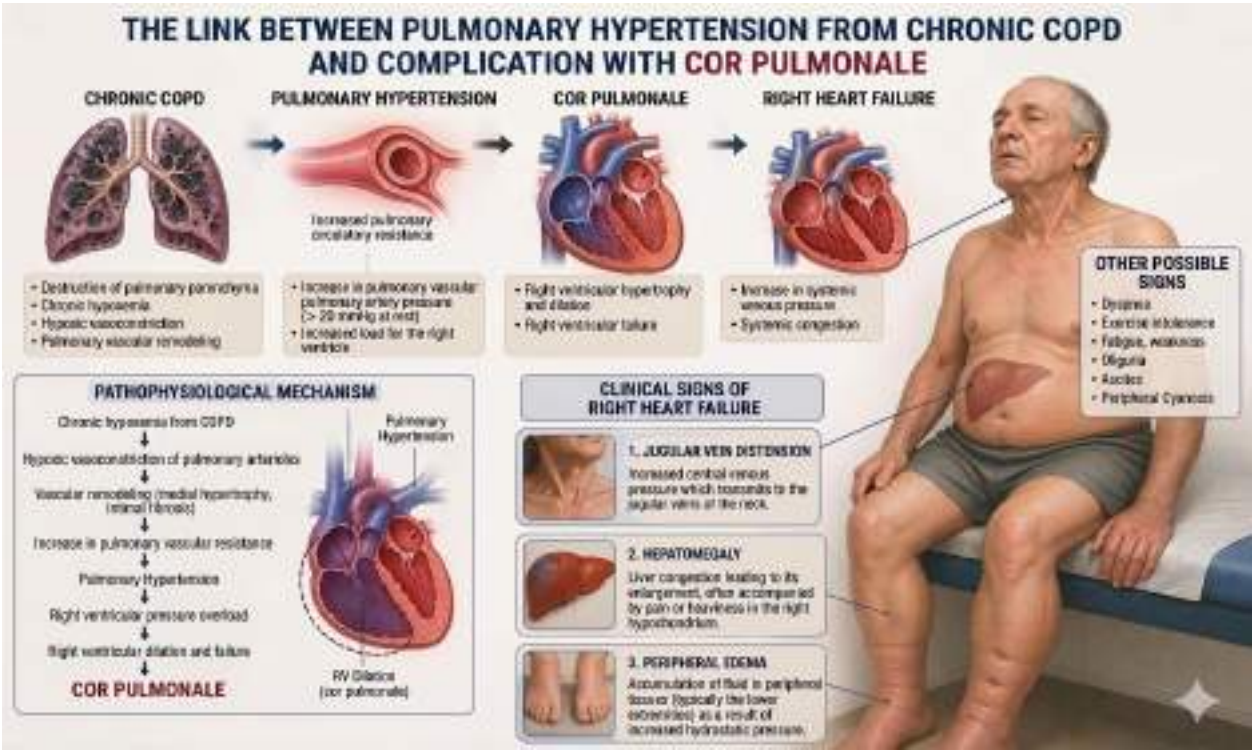

Figure 1. Pathophysiological link between chronic COPD-related pulmonary hypertension and Cor Pulmonale (Created by the authors based on literature data).

Analysis of Resistance and Adaptation: Contemporary literature, including studies by Gredic et al. (2020) and Sakao (2019), notes that the right ventricle is physiologically designed to work in a system with low pressure and high compliance. Unlike the left ventricle, the RV has a limited capacity to adapt to acute or chronic increases in "afterload" (opposing pressure). When mPAP exceeds the threshold of 20 mmHg, the VD begins to undergo initially adaptive changes (hypertrophy), which quickly turn into maladaptive (dilation and contractile failure).

Criticism of Traditional Treatments: One of the most critical aspects of the current literature is the failure of traditional pulmonary vasodilators (used for idiopathic PH) in patients with COPD and Cor Pulmonale. Studies show that drugs such as endothelin receptor antagonists or PDE5 inhibitors can be harmful in these patients, because by causing undifferentiated vasodilation, they "turn off" Hypoxic Pulmonary Vasoconstriction (HPV). This causes blood to go to unventilated areas, increasing the "shunt" and dramatically reducing oxygen saturation in peripheral blood.

The Emphysema Paradox: In the case of emphysema, the discussion becomes even more complex. Here, Cor Pulmonale is not only the result of pressure, but also of massive loss of the capillary bed and mechanical changes in the thorax. Recent literature suggests that the treatment of Cor Pulmonale in these patients should focus more on reducing lung volume (to reduce hyperinflation) and protecting the right ventricle through careful fluid management and diuretics, rather than aggressive vasodilators.

Prognostic Implications: The presence of Cor Pulmonale in the setting of COPD reduces the 5-year survival to less than 30%. A survival of 30% places Cor Pulmonale at a mortality level like many advanced forms of cancer, emphasizing the need for close monitoring and aggressive treatment of pathophysiological factors. This makes it necessary to identify early signs of RV failure through echocardiography and biomarkers such as NT-proBNP, long before the changes become irreversible.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the pathophysiology of PH in chronic obstructive disease is a multidimensional process, where genetic factors, exposure to tobacco, and failure of vascular regulatory mechanisms are combined. PH in COPD is not simply the result of oxygen deprivation, but of an interaction between chronic inflammation, vascular remodeling mediated by TGF-β, and parenchymal mechanical changes.
Some recommendations, after a critical analysis of the factors leading to PH, in the context of a chronic obstructive pathology, will be as follows:

- **Personalized Approach, as well as attention to Remodeling**: The future of therapy should shift from simple vasodilators towards "anti-remodeling" agents (such as Sotatercept) that aim to reverse the structural changes in blood vessels. The use of vasodilators should be done with the utmost care to avoid worsening the ventilation/perfusion ratio and severe hypoxemia.
- **RV Assessment**: Management of patients with chronic obstructive pathology should include regular monitoring of right ventricular function, as Cor Pulmonale remains the main factor dictating prognosis.
- **Prevention**: Smoking cessation remains the most effective intervention to stop the progression of inflammation and vascular remodeling before the installation of PH.

Acknowledgements: None declared

Conflict of interest: The authors declare no conflict of interest.

Author contribution. All authors contributed to the preparation of the manuscript and approved the final version.

REFERENCES

1. Chang, TC., Wang, CM., Ho, CH. et al. A prevalence study focusing on hospitalized COPD related pulmonary hypertension. Sci Rep 15, 12426 (2025). https://doi.org/10.1038/s41598-025-96629-9
2. Daniel M. Garrison et al. Cor Pulmonale. 2023, Treasure Island (FL): StatPearls Publishing
3. Nathan, S.D., Piccari, L., Abman, S.H., Balasubramanian, A., Girgis, R.E., Kovacs, G., Olschewski, H., Shlobin, O.A., Stockbridge, N., Wort, S.J., Washko, G.R. and Nikkho, S.M. (2025), Significance of Pulmonary Vascular Dysfunction in Chronic Obstructive Pulmonary Disease. Pulmonary Circulation, 15: e70144. https://doi.org/10.1002/pul2.70144
4. Chaouat, A. et al. Update on Pulmonary Hypertension in COPD. European Respiratory Review, 2020, 29(155), 200011.
5. Luca, E., Bodrug, N. The frequency of pulmonary hypertension in chronic obstructive pulmonary disease of geriatric patients: a narrative literature review. Egypt J Intern Med 34, 47 (2022). https://doi.org/10.1186/s43162-022-00135-7
6. Yogeswaran A, Kuhnert S, Gall H, Faber M, Krauss E, Rako ZA, Keranov S, Grimminger F, Ghofrani HA, Naeije R, Seeger W, Richter MJ, Tello K. Relevance of Cor Pulmonale in COPD With and Without Pulmonary Hypertension: A Retrospective Cohort Study. Front Cardiovasc Med. 2022 Feb 16;9:826369. doi: 10.3389/fcvm.2022.826369.
7. Seiichiro Sakao, Chronic obstructive pulmonary disease and the early stage of cor pulmonale: A perspective in treatment with pulmonary arterial hypertension-approved drugs, Respiratory Investigation, Vol 57, Issue 4,2019, Pages 325-329, ISSN 2212-5345, https://doi.org/10.1016/j.resinv.2019.03.013.
8. Gredic M, Blanco I, Kovacs G, et al. Pulmonary hypertension in chronic obstructive pulmonary disease. Br J Pharmacol. 2021;178:132–151. https://doi.org/10.1111/bph.14979
9. Shujaat A, Minkin R, Eden E. Pulmonary hypertension and chronic cor pulmonale in COPD. Int J Chron Obstruct Pulmon Dis. 2007;2(3):273-82.
10. Wang, Y. et al. Pulmonary Hypertension in COPD: Correlation with Airway Obstruction. Respiratory Research, 2017, 18(1), 122.
11. Patel, A. et al. FEV1 and Pulmonary Pressures in Advanced COPD. Chest, 2018, 154(4), 837–845.