

REVIEW

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The frequency of pulmonary hypertension in chronic obstructive pulmonary disease of geriatric patients: a narrative literature review

Ecaterina Luca* and Nicolae Bodrug

Abstract

Background: Pulmonary hypertension (PH) is a serious complication with complex pathogenesis in the natural history of chronic obstructive pulmonary disease COPD, with a progressively increasing frequency with a meanwhile decreasing in functional capacity.

Purpose: Assessment of the incidence, pathogenesis, peculiarities, and complications of PH in COPD in geriatric population worldwide.

Methods: We performed an analysis of randomized, retrospective, and prospective clinical, case-control and observational studies, published at the international level, according to the subject studied and target population. Four hundred ninety-seven full articles were identified after the search through engine Google Search and databases PubMed, Hinari, SpringerLink, and Scopus (Elsevier) according to the keywords and subsequent filters.

Results: Depending on various factors, like the population examined, the definition used for mPAP (mPAP > 20 mm Hg or ≥ 25 mm Hg), the severity of the lung disease, and the method of measuring PAP, a varied incidence of COPD patients with PH complication was discovered, namely 10–91%. PH prevalence increases with the COPD severity. The presence of PH is associated with acute exacerbations of COPD, reduced survival, and increasing expenses for health-care programs. Mild to moderate levels of PH (mPAP 25–34 mm Hg) are relatively common in COPD and usually are associated with severe airflow obstruction or parenchymal destruction. Only a minority of patients (1–5%) have severe PH (mPAP ≥ 35 mm Hg).

Conclusions: Diagnosis of PH in COPD is difficult, especially in a mild form, and requires a clinical approach associated with a comprehensive set of investigations for confirming the etiology, evaluation of the functional and hemodynamical impairment severity, and important factors in the appropriate treatment election.

Keywords: Pulmonary hypertension, Chronic obstructive pulmonary disease, Geriatric patients, Acute exacerbation, Echocardiography

Background

Pulmonary hypertension (PH) is a serious, progressive condition characterized by endothelial dysfunction and vascular remodeling, which leads to increased

mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance, and eventually right ventricular dysfunction (RV) [1, 2]. PH is a clinically relevant problem in chronic obstructive pulmonary disease (COPD) due to its high prevalence and its impact on morbidity and mortality [3].

COPD is the leading cause of chronic respiratory failure, PH and cor pulmonale, complications that are recorded in 80–90% of cases [4–6]. PH is a common

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complication that develops secondarily and slowly in the natural course of COPD patients and is associated with the development of severe chronic hypoxemia that induces pulmonary vascular remodeling. The severity of PH correlates with the degree of airflow obstruction and impaired alveolar-capillary diffusion. PH is a major cardiovascular complication of COPD, associated with the development of RV hypertrophy and/or dilation, right heart failure (pulmonary heart disease), and poor prognosis: increased rates of exacerbation, hospitalization, and mortality [3, 5–10].

The most severe heart complication of chronic lung disease is cor pulmonale, characterized by hypertrophy and/or dilation of RV with the further development of right heart failure, caused by PH, which in turn is caused by primary impairment of function and/or of the lung structure [1, 5, 8, 9, 11–13].

Therefore, PH is a progressive condition defined by the remodeling of small lung vessels and increased pulmonary vascular resistance, which can eventually lead to right heart failure. PH is determined to assess the prognosis of COPD, which is estimated to become the fourth leading cause of death by 2030 [14].

The *aim* of this study was to appraise the peculiarities of pulmonary hypertension in elderly patients with COPD worldwide, for planning effective interventions and properly allocating the health resources in the Republic of Moldova [15, 16].

Search strategy and selection criteria

In order to achieve the stated objective, the initial search of the specialized scientific literature, identified by the search engine Google Search and from the databases PubMed, Hinari, SpringerLink, and Scopus (Elsevier), was performed. The publications were selected according to the following keywords: “pulmonary hypertension,” “chronic obstructive pulmonary disease,” “acute exacerbation,” “elderly,” and “echocardiography.” After processing the information in the databases, we selected all publications in English starting with January 1990.

For the advanced selection of bibliographic sources, the following filters were applied: full-text articles, articles in English, and articles published during the years 1990–2021. After a preliminary analysis of the titles, original articles, editorials, articles of narrative, systematic synthesis, and meta-analysis, the articles that contained relevant information and contemporary concepts about pulmonary hypertension in elderly patients with COPD were selected. Additionally, a search was performed in the bibliographic reference lists of the identified sources in order to highlight relevant additional publications, which were not found during the initial search in the

databases. A total of 497 full articles were identified according to search criteria. The final literature contains 34 relevant sources that have provided information on pulmonary hypertension in elderly patients with COPD.

Results

Pulmonary hypertension is a hemodynamic and pathophysiological condition characterized by an increase in mPAP ≥ 25 mm Hg at rest or ≥ 30 mm Hg at physical exertion, measured by right cardiac catheterization [1, 2].

The epidemiology of pulmonary hypertension

Estimates of PH prevalence in patients with COPD are not well established, as right cardiac catheterization is not usually performed in this group of patients, and echocardiography is subjected to diagnostic limitations. Estimation is further impaired by the use of a variety of different limit values for establishing PH in previous studies [1].

The prevalence of PH secondary to COPD varies depending on the definition, the groups of patients studied, and the method of estimating PH. However, most studies used non-invasive measurements to estimate PAP. There is no clear and accurate information on the prevalence of PH in the group of patients with mild COPD. Depending on the population examined, the definition used (mPAP > 20 mm Hg or ≥ 25 mm Hg), the severity of the lung disease (maximum expiratory volume per second), and the method of measuring PAP (echocardiography or right cardiac catheterization), 10–91% of patients with COPD shows PH [4, 6, 9, 11]. The prevalence of PH, determined by echocardiography, in patients with COPD of varying severity was 38.02–62.4% [17, 18], including mild grade 37.6%, moderate grade 10.1%, and severe grade 14.7% [18]. The minimum prevalence of PH in patients with at least 1 hospitalization for COPD was 10–30%, and among patients with advanced COPD—20% [19]. Studies in large cohorts of COPD patients with right cardiac catheterization reported a prevalence of PH of 50.2% in patients with advanced disease requiring surgery to reduce lung volume [11] and 30–70% in patients with advanced cardiac catheterization. Patients in the final stage of the disease were evaluated for lung transplantation [2, 20].

In patients with COPD without exacerbations in the last 2 months before inclusion in the study, without left ventricular dysfunction (LV), and without comorbidities, the prevalence of PH (mPAP at rest ≥ 25 mm Hg) was 27%. The prevalence of PH increases according to the stage of COPD: 5% in patients with moderate COPD (GOLD II), 27% in patients with severe COPD (GOLD III), and 53% in patients with very severe COPD (GOLD IV) [14].

The pathogenesis of pulmonary hypertension in COPD is complex and has many aspects. The development of PH in COPD patients is usually conditioned by a combination of several factors, which may have a direct or indirect impact on pulmonary hemodynamics. Hypoxia and endothelial dysfunction play a central role in the development of PH [3, 4, 6, 9, 11, 14].

The mechanisms of pulmonary vascular change, which occur in smokers with normal lung function and in the early stages of COPD, are chronic hypoxemia, systemic inflammation, and the effect of cigarette smoke. Secondary PH to COPD is characterized by (1) vascular remodeling (hypertrophy, proliferation, or change in the phenotype of contractile cells; endothelial dysfunction—thickening of the intima with loss of endothelial cell function and decreased luminal diameter, resulting in smooth muscle cell proliferation and tissue accumulation and contractile function in the pulmonary arteries and arterioles; systemic inflammation), (2) destruction of the pulmonary vascular bed by emphysema with reduction of the total number of pulmonary vessels and increase of pulmonary vascular resistance, and (3) pulmonary thrombosis. All these mechanisms contribute to hypoxic pulmonary vasoconstriction [3, 4, 6–11, 14, 19]. PH is thought to develop in COPD patients by reducing the pulmonary vascular bed by more than 50% or by destroying the lung parenchyma by more than 2/3 [18].

PH secondary to COPD may be proportionate or disproportionate (PAP at rest ≥ 35 mm Hg). Proportional PH is based on the assumption that the underlying parenchymal remodeling process, accompanied by hypoxia, results in an increase in pulmonary vascular resistance, leading to a “natural” loss in the area of the total vascular cross-section. Disproportionate PH is the sudden development of PH from lung parenchymal lesions. These patients have reduced airway obstruction, more severe hypoxia, and reduced ability to diffuse carbon dioxide [5, 7, 9, 14].

Therefore, the causes of increased pulmonary vascular resistance (stiffness) in patients with PH secondary to COPD include pulmonary vascular remodeling, endothelial dysfunction, inflammation, hypoxic vasoconstriction, destruction of the parenchyma and pulmonary vascular bed, and hyperinflation [8, 10, 19, 21]. There is widespread agreement that chronic alveolar hypoxia contributes to the development of PH through two mechanisms: (1) hypoxic acute pulmonary vasoconstriction of small muscular pulmonary arteries with a substantial increase in pulmonary vascular resistance; (2) pulmonary vascular remodeling with thickening of the intima and neomuscularization of small pulmonary arterioles with

a substantial increase in pulmonary vascular resistance [8, 10, 19].

Human and experimental animal data show that PH in COPD patients is likely to be a direct result of tobacco smoke damage to abnormally produced intrapulmonary vessels by mediators that control vasoconstriction, vasodilation, and vascular cell proliferation, leading to reshaping and aberrant vascular physiology [22].

The pathophysiology of pulmonary hypertension in COPD, but also in chronic lung diseases, is complex and multifactorial. Blocked pulmonary capillary pressure, cardiac output, and pulmonary vascular resistance are responsible for increased PAP. Many structural and functional factors, which affect different areas of the pulmonary vascular system, are responsible for the development of PH in COPD. These are the main factors that lead to chronic inflammation, vasoconstriction, vascular remodeling, and, consequently, PH. In addition, pulmonary vascular resistance increases with restricted airflow, hypoxemia, hypercapnia, acidosis, polycythemia, and systemic inflammation [7–11, 14, 19, 23].

Alveolar hypoxia is one of the most important causes of increased pulmonary vascular resistance. Acute alveolar hypoxia causes hypoxic pulmonary vasoconstriction in the smooth muscles of the small pulmonary arteries with increasing pulmonary vascular resistance and PAP. Hypoxic pulmonary vasoconstriction is a defensive mechanism that reduces perfusion in poorly ventilated or unventilated lung areas, redirects blood to more ventilated areas, restores ventilation-infusion balance, and maintains blood oxygen levels. Thus, chronic hypoxia, by increasing the tone of the pulmonary artery, inducing angiogenesis, vascular remodeling, and increasing blood viscosity secondary to polycythemia, contributes to the installation of PH [1, 6, 7, 9–11, 14, 19].

Although hypoxia makes an important contribution to the development of PH secondary to COPD, this is not the only factor. R&D dysfunction, peripheral edema, and physical exertion are important in the pathophysiology of PH [6, 14].

PH's anatomical and pathophysiological changes include:

1. Increased PAP contributes to increased RV pressure, RV wall distension with LV diversion of the interventricular septum, filling impairment and increased LV filling pressure, and, as a result, LV systolic and diastolic dysfunction.
2. Chronic progressive pressure loading contributes to the remodeling of RV (initially hypertrophy and later dilation) with the onset of RV insufficiency [8–11, 14, 19, 23].

The classification of pulmonary hypertension

The PH clinical classification, updated in 2013, includes 5 broad categories with common pathogenetic mechanisms. PH caused by lung diseases is “class III: pulmonary hypertension due to lung disease and/or hypoxia,” which is one of the most common forms of PH, COPD being the main cause [10, 14, 24].

In previous guidelines of the European Society of Cardiology and the European Respiratory Society (2009 and 2015) and at the 6th World Symposium on Pulmonary Hypertension (2018), it was stated that mPAP at rest is 14.0 ± 3.3 mm Hg, the limit upper—20 mm Hg, and normal values range from 8 to 20 mm Hg. The mPAP value ≥ 25 mm Hg, measured by cardiac catheterization at rest, is defined as PH. In older studies, PH was defined as mPAP > 20 mm Hg [4, 5, 7, 10, 11, 14, 21, 25, 26].

Recently, the 6th World Symposium on Pulmonary Hypertension (2018) recommended the following hemodynamic classification of PH in COPD patients:

1. COPD without PH: mPAP <21 mm Hg or mPAP 21–24 mm Hg with pulmonary vascular resistance <3 wooden units.
2. COPD with PH: mPAP 21–24 mm Hg with pulmonary vascular resistance ≥ 3 wooden units or mPAP 25–34 mm Hg.
3. COPD with severe PH: mPAP ≥ 35 mm Hg or mPAP ≥ 25 mm Hg with low heart rate - <2.0 l/min/m² [1, 8–10, 25, 27].

In most patients with stable COPD, PH is mild to moderate (mPAP 25–34 mm Hg), even in patients with advanced disease. Only a minority of patients (1–5%) have severe PH (mPAP ≥ 35 mm Hg) [7, 10, 19, 21, 27, 28]. A mPAP ≥ 40 mm Hg is very rare in COPD and requires specification of another cause of PH (left heart disease, sleep apnea syndrome, pulmonary embolism, etc.) [11].

Diagnosis of pulmonary hypertension in COPD is difficult, especially in a mild form, and requires clinical suspicion based on the clinical picture, subjective symptoms, objective examination, disease history, and history with a comprehensive set of investigations to confirm hemodynamic criteria for etiological functional and hemodynamic severity [2, 10, 19, 25]. The diagnosis of PH involves two stages: detection (determination of the cause of symptoms or PH in a high-risk patient) and characterization (determination of the specific clinical context of PH, including causative factors, associated diseases, hemodynamic disorders and their location and sequelae) [25, 29].

The clinical symptoms of PH in COPD patients are subtle, nonspecific, and difficult to distinguish from the

clinical manifestations of COPD. Therefore, it is difficult to clinically diagnose PH secondary to COPD. The main symptoms are mostly dyspnea and exercise intolerance. Coughing and sputum production caused by COPD and smoking are common in the patient’s history. The first suspicion is the presence of peripheral edema caused by RV dysfunction. Hemoptysis following the rupture of the bronchial artery, dysphonia caused by compression of the left laryngeal nerve of the dilated pulmonary artery, wheezing, chest pain, and/or ischemic heart disease caused by coronary artery occlusion are other charges [2, 6, 8–10, 14, 19, 25, 28, 30].

Diagnostic methods

Imaging examination findings (radiography, computed tomography, magnetic resonance imaging) are insufficient for the diagnosis of PH secondary COPD. Pulmonary artery trunk dilation (≥ 25 mm), increase in the pulmonary hilum, right atrium dilation, and RV dilation in advanced COPD are identified [2, 4, 6, 8–11, 14, 19, 25].

Lung function tests and arterial blood sampling are required for the differential diagnosis of underlying lung disease (respiratory or parenchymal). In the arterial blood gases of COPD patients, PaO₂ is low, and PaCO₂ is normal or high. Hypoxic pulmonary vasoconstriction begins at PaO₂ <55–60 mm Hg [11, 14, 25]. Chronic hypercapnia increases the risk of developing PH due to acidosis. As airway obstruction progresses, expired peripheral airways may collapse more easily, which contributes to increased intraalveolar pressure and PH [11, 14].

The following changes suggest the presence of PH on *electrocardiography*: (1) P-pulmonary wave (dilation of the right atrium) in leads II, III, and aVF; (2) findings of RV hypertrophy: right deviation of the electrical axis of the heart > 120°, increasing the amplitude of the R wave in the V1 lead and the R / S ratio <1 in the V5-6 leads; (3) the electric axis of the heart S1-S2-S3; (4) the electric axis of the heart S1-Q3; (5) incomplete/complete right branch block of the His bundle; (6) depolarization anomalies in the precordial and inferior derivations; and (7) increase in QRS wave amplitude and prolonged QT segment. At least two of these criteria are sufficient to suspect RV hypertrophy [2, 4, 6, 9, 11, 14, 19, 25].

Transthoracic echocardiography with Doppler examination is the first non-invasive method for diagnosing PH and COPD patients; it is very feasible and useful and is therefore a potential screening tool, despite technical difficulties (pulmonary hyperinflation). The method is used to diagnose PH in 99% of medical institutions [1, 4, 6–14, 19, 31, 32].

Echocardiography plays a central role in the primary assessment of RV morphology and function in all forms of PH, providing an accurate perspective on

pathophysiological changes and bearing important diagnostic and prognostic value [2, 13]. Echocardiography allows the evaluation of RV hypertrophy and/or dilation, the dynamics of the heart ejection fraction and provides direct and indirect data on the growth of PAP, its etiology, and prognosis. The pulmonary trunk appears dilated (the ratio between the diameter of the lung trunk and that of the aorta > 1 is a sign of dilation of the lung trunk). However, in the early stages of the disease, the data may be normal, and in the more advanced stages, due to pulmonary hyperinflation and right heart rotation, it is difficult to clearly visualize the heart structure and narrow the “echocardiographic window” [4, 6–14, 19, 31, 32].

The correlation between PH values determined by right cardiac catheterization and echocardiography has been confirmed in many studies [33]. Although some studies describe the underestimation or overestimation of PAP by echocardiography, a meta-analysis showed that the method has good sensitivity (83%), reasonable specificity (72%), and a correlation of 0.7 with invasive measurements. Most deviations from right cardiac catheterization measurements occur in patients with severe PH [17]. However, transthoracic echocardiography is certainly a valid screening tool for PAP classification [32].

When there is a chronic increase in RV pressure in patients with PH, two-dimensional echocardiography may detect RV dilation, RV hypertrophy (norm - < 4 – 5 mm, in severe PH RV wall thickness may reach 6 – 8 mm), interventricular septal thickening, change in the ratio between the thickness of the interventricular septum and the thickness of the posterior wall of LV > 1 , global systolic RV dysfunction, pressure gradient of tricuspid regurgitation, and systolic excursion of the plane of the tricuspid ring. Doppler echocardiography is one of the most informative non-invasive methods of estimating PAP; it can determine systolic, diastolic, and mean pressure in the pulmonary artery [8, 10, 12–14, 19].

Right heart catheterization is the reference method and “gold standard” for the most accurate determination of PH and is used in 36% of medical institutions. However, the method is rarely performed in patients with COPD, except in cases of (1) confirmation or exclusion of the diagnosis of PH in patients requiring transplantation or reduction in lung volume, (2) suspicion of severe PH, (3) repeated episodes of insufficiency of VD, and (4) uncertain echocardiographic data with clinical indications of PH coexistence. There are currently no studies demonstrating the clinical utility of cardiac catheterization in the routine evaluation of COPD [1, 2, 4, 6, 7, 9–11, 14, 29, 32].

Right cardiac catheterization allows the evaluation of RV hypertrophy and/or dilation and the measuring of

central venous pressure, right atrium pressure, RV pressure, PAP, and blocked pulmonary capillary pressure. The method also allows the evaluation of the pulmonary gradient, the cardiac output, the pulmonary vascular resistance, and the testing of vasoreactivity in the pulmonary circulation. However, the method does not apply to every COPD patient because it is an invasive examination [1, 2, 6, 7, 9, 11, 12, 79, 32].

Cardio-pulmonary stress tests are used to assess functional capacity. PH is triggered by physical exertion in 90% of cases and mPAP can be doubled by physical exertion, regardless of whether or not there is resting PH. PH should be considered, especially in patients with reduced exercise capacity not associated with symptoms [7, 14].

The 6-min walk test is a lower-cost, reproducible form developed in 1963. Before and after the test, heart rate, blood pressure, dyspnea, and oxyhemoglobin levels are recorded according to the Borg scale [14]. PH in COPD patients is associated with limited exercise capacity [8].

Natriuretic proteins

There is no biochemical marker for PH secondary COPD screening. Natriuretic proteins, BNP, and its precursor NT-proBNP are elevated in the presence of acute exacerbation of COPD (increased PH) and in the presence of severe PH. However, their specificity is low, as the concentration of BNP and NT-proBNP also increases in patients with cardiovascular disease [2, 4, 7, 10, 14]. However, plasma natriuretic proteins, especially elevated levels during monitoring, are an independent predictor of mortality in patients with primary PH [34].

Prognosis of pulmonary hypertension

Several studies have shown that patients with COPD and PH have reduced survival. In patients with COPD and severe PH, survival at 1 year was 70% and survival at 3 years—33%, significantly lower compared to 83% and 55%, respectively, observed in patients with COP with mild PH to moderate [8].

Unfortunately, to date, there is no specific treatment and we do not have adequate therapeutic alternatives for the treatment of PH in patients with COPD, and the drugs available for supportive treatment are limited. The treatment of choice for patients with COPD and PH is long-term oxygen therapy [2, 10].

Conclusions

1. PH is a serious complication in the natural history of COPD, increasing progressively, while functional capacity gradually decreases. Although the pathogenesis of PH is complex, it often involves hypoxic

pulmonary vasoconstriction and pulmonary vascular remodeling.

- Depending on the population examined, the definition used (mPAP > 20 mm Hg or ≥ 25 mm Hg), the severity of lung disease (FEV1), and the method of measuring PAP (echocardiography or right cardiac catheterization), 10–91% of COPD patients have PH. PH's prevalence increases with COPD.
- The presence of PH is associated with acute exacerbation of COPD and reduced survival and is a major factor in the use of health resources. Mild to moderate levels of PH (mPAP 25–34 mm Hg) are relatively common in COPD, usually associated with severe airflow obstruction or parenchymal destruction. Only a minority of patients (1–5%) have severe PH (mPAP ≥ 35 mm Hg).
- Diagnosis of PH in COPD is difficult, especially in a mild form, and requires clinical suspicion based on the clinical picture, subjective symptoms, objective examination, disease history, and history of reviewing a comprehensive set of investigations to confirm hemodynamic criteria and to determine the etiology, functional, and hemodynamic severity.

Abbreviations

COPD: Chronic obstructive pulmonary disease; HF: Left heart failure; LV: Left ventricle; RV: Right ventricle; PH: Pulmonary hypertension; mPAP: Mean pulmonary arterial pressure; AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; CVD: Cardiovascular disease; FEV1: Forced expiratory volume; NP: Natriuretic proteins; NT-proBNP: Terminal fragment of natriuretic protein type B.

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Authors' contributions

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Competing interests

The authors declare that they have no competing interests.

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