Pulmonary vascular disease in chronic lung diseases – cause or comorbidity?

Disorders of the Pulmonary Circulation section

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IB: Conceptualisation, formal analysis, methodology, writing (original draft, review and editing). RTC: Conceptualisation, formal analysis, methodology, writing (original draft, review and editing). JAB: Conceptualization, supervision, formal analysis, writing (review and editing).

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ABSTRACT (200 words)

Purpose of review: To provide timely and relevant insights into the complex relationship between pulmonary vascular disease (PVD) and chronic lung disease (CLD), focusing on the causative and consequential dynamics between these conditions. **Recent findings**: There are shared pathogenic mechanisms between pulmonary arterial hypertension (PAH) and Group 3 pulmonary hypertension (PH), including altered expression of mediators and growth factors implicated in both conditions. Factors such as hypoxia, hypoxemia, and hypercapnia also contribute to pulmonary vascular remodelling and endothelial dysfunction. However, the role of hypoxia as the sole driver of PH in CLD is being reconsidered, particularly in chronic obstructive pulmonary disease (COPD), with evidence suggesting a potential role for cigarette smoke products in initiating pulmonary vascular impairment. On the other hand, interstitial lung disease (ILD) encompasses a group of heterogeneous lung disorders characterized by inflammation and fibrosis of the interstitium, leading to impaired gas exchange and progressive respiratory decline, which could also play a role as a cause of PH. **Summary:** Understanding the intricate interplay between the pulmonary vascular compartment and the parenchymal and airway compartments in respiratory disease is crucial for developing effective diagnostic and therapeutic strategies for patients with PVD and CLD, with implications for both clinical practice and research.

Keywords: *Pulmonary hypertension; lung diseases; chronic obstructive pulmonary disease; interstitial lung disease*

Introduction

Pulmonary hypertension (PH) can be associated with chronic respiratory disease, particularly with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) (1). In such scenarios, the existence of PH correlates with diminished survival rates and an unfavorable clinical trajectory (2,3). The prevalence of PH in respiratory diseases cannot be overlooked, as it may approach 50% or even higher in patients with advanced disease (4,5).

PH associated with lung diseases, classified as group 3 in the current PH classification, denotes a progressive aspect of the disease marked by elevated pulmonary arterial pressure (PAP) (pre-capillary PH) (4). The proceedings of the 6th World Symposium on PH, held in Nice in 2018, recognize that a mean pulmonary arterial pressure (mPAP) exceeding 20 mmHg should be deemed abnormal (1) and recommend revising definitions to capture better the presence of pulmonary vascular dysfunction (PVD). It was proposed that a pulmonary vascular resistance (PVR) threshold be incorporated to more precisely gauge the impact of PVD on PH. The severity of PH is contingent upon hemodynamic observations. According to the most recent PH guidelines of the European Society of Cardiology (ESC)-European Respiratory Society (ERS) (6), PH associated with lung disease is defined by a mean PAP >20 mmHg and pulmonary vascular resistance (PVR) >2 WU.

Pulmonary vascular disease is not solely a consequence of the underlying lung disease; it can emerge and advance autonomously (7). In some instances, PH takes precedence in the clinical profile of patients (7,8). To characterize this presentation, the term "pulmonary vascular phenotype" has been introduced. Consequently, the 2022 ESC/ERS guidelines, changed the terminology of group 3 PH from “Pulmonary hypertension due to lung disease and/or hypoxia” to “Pulmonary hypertension associated with lung disease and/or hypoxia” (6).

In a recent metanalysis, the pooled prevalence of PH associated with COPD was 39.2% (5). Severe PH, defined by mPAP >20mmHg and PVR >5 WU (9–11), is rare in chronic respiratory

diseases; it manifests in approximately 7% of COPD patients (5) and less than 10% of patients with ILD. In idiopathic pulmonary fibrosis (IPF), an initial assessment has shown that mean pulmonary arterial pressure (mPAP) equal to or greater than 25 mmHg is present in 8–15% of patients. The prevalence of this condition escalates notably in advanced stages, ranging from 30 to 50%, and increases further in end-stage disease, exceeding 60% (11–13). In patients with chronic hypersensitivity pneumonitis, small-scale studies have documented pulmonary hypertension in 20–44% of cases (14,15). Similarly, in one study, 20% of individuals with interstitial lung disease (ILD) associated with connective tissue disease were found to have PH (16). Patients diagnosed with group 3 PH face the most unfavorable prognosis among the various forms of PH (2,17). The presence of comorbidities is intricately linked to poorer health outcomes, requiring more complex clinical management and leading to increased healthcare costs (18,19).

Comorbidity is typically defined in reference to a specific primary condition (20), as outlined in Feinstein's influential definition: "Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study." (21) However, determining which condition should be considered the primary index and which should be classified as comorbid is not always straightforward. It may vary depending on factors such as the research focus, the disease prompting a particular episode of care, or the specialty of the attending physician. In the case of respiratory and vascular diseases, it often remains unclear whether a disease is the cause or consequence, especially if the diagnosis is delayed. This delay can have implications not only for diagnosis but also for therapy, which may affect prognosis. The aim of this review is to discuss whether PH serves a cause or consequence in the different chronic lung diseases with which it is associated.

Common pathophysiology in group 3 PH

Physiologically, in the lungs, circulation operates within a low-pressure system. Predominantly, resistance arises from the intrinsic narrowing of pulmonary vessels as they

bifurcate from central arteries. In instances of increased cardiac output during stress, the pulmonary vasculature can adapt by dilating to accommodate elevated blood volumes, with previously underutilized arteries being engaged (22). Consequently, PAP typically undergoes minimal fluctuations.

In people with chronic lung diseases, a notable diminishment in the number of blood vessels occurs, thereby impairing the capacity to accommodate heightened cardiac output, consequently resulting in elevated pressures (22). Furthermore, most severe, and enduring lung conditions are characterized by periods of sustained or intermittent hypoxia. Unlike systemic circulation, the pulmonary vasculature responds to alveolar hypoxia by constricting. Prolonged exposure to hypoxia prompts the release of vasoconstrictive agents such as endothelin and serotonin, which also possess proliferative properties (23). This cascade precipitates intimal hyperplasia and medial hypertrophy, ultimately culminating in increased vascular tone (22).

Endothelial cells respond to hypoxemia by diminishing nitric oxide levels while elevating endothelin-1 concentrations (24,25). Consequently, smooth muscle cell contraction occurs, and cellular proliferation is heightened through the suppression of anti-mitogenic factors such as nitric oxide and prostacyclin, alongside an increase in the production of various mitogenic stimuli including platelet-derived growth factor and vascular endothelial-derived growth factor (26).

Chronic obstructive pulmonary disease (COPD)

COPD is defined as a heterogeneous lung condition characterised by chronic respiratory symptoms (dyspnoea, cough, expectoration and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction (22). Recent research revealed that both the severity of airflow limitation and pulmonary vascular disease independently and significantly contributed to

increased mortality, with similar impact (3). This finding lends support to the notion that smoking, aging, and other factors initiating both endothelial and epithelial dysfunction set off various pathological mechanisms that eventually limit life expectancy (Figure 1) (3,23).

Changes in vessel structure are widespread, and abnormalities in their function impair gas exchange, which also contributes to PH, a key factor linked to decreased survival in COPD (4). Research revealing endothelial dysfunction in the early stages of the disease has contributed to our comprehension of pathogenesis of PH in COPD and unveiled a potential novel approach for its treatment (24,25).

Cigarette smoke has been shown to directly disturb factors involved in vascular remodeling. This includes reducing endothelial nitric oxide synthase (eNOS) expression, increasing oxidative stress within mitochondria, and decreasing prostacyclin synthase mRNA signaling and protein expression (26). Furthermore, in COPD the marked impairment of gas exchange is explained by the concurrence of severe ventilation-perfusion (VA/Q) mismatch (27) and altered hypoxic vasoconstriction, however the molecular pathways governing vascular remodelling, typically associated with PAH, are also frequently observed in PH associated to COPD (PH-COPD). These mechanisms involve endothelial cell dysfunction, fibroblast proliferation, and dysregulated angiogenesis (26).

Research involving explanted lungs from COPD patients undergoing lung transplantation revealed evidence of the diversity of these processes. Patients with severe pulmonary hypertension due to COPD exhibit pulmonary vascular remodelling in both resistance arteries and precapillary vessels, and reduced capillary density compared to those with moderate pulmonary hypertension due to COPD and to those without pulmonary hypertension (28–30). Another study that employed quantitative computed tomography (CT) pulmonary vessel analysis, indicated that the pulmonary vessel volume in individuals with PH due to COPD correlates with the severity of PH and mortality risk (31).

Interstitial lung disease (ILD)

PH associated with interstitial lung disease (PH-ILD) is frequently encountered, with an estimated prevalence ranging from 10% to 80% among patients diagnosed with idiopathic pulmonary fibrosis (IPF) and is similarly prevalent in other fibrotic interstitial lung diseases (ILDs) (1,32). Numerous studies have consistently shown that the onset of PH correlates with significant morbidity and diminished survival rates (1,32,33).

Various underlying conditions can trigger or exacerbate PH in ILD. Upon confirming a PH diagnosis, it becomes essential to identify any coexisting conditions, which may either directly cause or contribute to PH (34). Addressing these conditions with appropriate therapies could alleviate symptoms and enhance the overall quality of life (QoL) (34). Among the conditions warranting consideration are emphysema (35), sleep-related breathing disorders such as obstructive sleep apnoea (OSA) (36), heart disease (37), and acute or chronic thromboembolic disease (38).

In explanted lung samples obtained from individuals with IPF, vascular remodelling was observed in regions where the lung architecture remained intact (39). Additionally, CT scan revealed that the presence of pulmonary vascular pruning correlated with a higher risk of interstitial lung abnormalities, and this phenomenon could be detected before objective interstitial remodelling occurred (40).

Shared pathogenic mechanisms between PAH and group 3 PH

Numerous mediators and growth factors implicated in the pathogenesis of PAH exhibit altered expression in PH associated with chronic lung diseases (7). Factors such as vascular endothelial growth factor, endothelin-1, interleukin-6, transforming growth factor-β, tumour necrosis factor-α, and impaired endothelial nitric oxide synthase (eNOS) activity have all been implicated in smoking-related lung diseases and the development of emphysema or ILD (7).

Mounting evidence suggests that smoking not only contributes to airway and parenchymal damage but also directly contributes to pulmonary vasculopathy (Figure 1) (41–44).

Additionally, the presence of a heterogeneous distribution of capillary density, characterized by focal areas of proliferation, is recognized in PAH, particularly when pulmonary veins and capillaries are prominently affected, a condition termed pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (45). Studies have documented that in lungs afflicted with idiopathic pulmonary fibrosis (IPF), pulmonary veins exhibit constrictive remodelling not only in fibrotic regions but also in preserved areas, even in the absence of remodelling in the pulmonary arteries (39).

The mechanisms that promote the development of PH are explained in Figure 1 and include the combined effects of hypoxia, pulmonary dysfunction with air trapping, and the toxic effects of cigarette smoke leading to inflammation, endothelial dysfunction, and angiogenesis (46,47).

Relationship between respiratory pathophysiology of lung diseases and PH

There are factors that collectively promote pulmonary vascular remodelling by causing endothelial dysfunction and facilitating the proliferation of pulmonary vascular smooth muscle cells and endothelial cells (7). Hypoxia, hypoxemia, and hypercapnia are known contributors to PH in chronic lung diseases, although their specific impact on pulmonary vascular remodelling remains uncertain (48,49). Furthermore, pulmonary arterial vasoconstriction can persist due release of vasoactive peptides, to shifts in nitric oxide balance, and changes in potassium and calcium channel flux properties within smooth muscle cells (50). Particularly, hypoxia has traditionally been regarded as the primary pathogenic mechanism of PH in COPD (4). Nevertheless, its role is undergoing reconsideration due to the observation of pulmonary vascular remodelling and endothelial dysfunction in patients with mild COPD who lack hypoxemia, as well as in smokers with normal lung function (51,52). Additionally, the fact that

long-term oxygen therapy (LTOT) does not completely reverse pulmonary hypertension further challenges the notion of hypoxia as the sole driver of PH in COPD (53).

Observations from our research group suggest that cigarette smoke products may play a role in initiating pulmonary vascular impairment in COPD (24). This contention stems from the observation that even smokers with normal lung function exhibit pulmonary artery remodelling (52), endothelial dysfunction (25), reduced expression of eNOS (54), increased VEGF expression (43), and inflammatory cell infiltration, mirroring findings observed in patients with mild-to-moderate COPD but distinct from nonsmokers.

On the other hand, there are other different mechanisms that can explain the increase in PAP in COPD: (I) lung hyperinflation, which leads to elevated thoracic pressure readings and a reduction in blood volume within all cardiac chambers. This diminishes stroke volume while increasing sympathetic drive; (II) enhanced filling pressure within the left ventricle due to systolic, diastolic, or combined heart failure (HF). This results in an elevated pulmonary arterial pressure even when PVR remains normal; (III) elevated PVR, leading to both an increased transpulmonary arterio-venous pressure gradient and, in severe instances, a reduction in cardiac output (CO) (55).

Comorbidity and PAH

There is uncertainty regarding whether patients with lung diseases (COPD or ILD) with severe PH exhibit a unique pulmonary vasculopathy or simply the concurrent presence of idiopathic PAH and lung disease, a common scenario. Intriguingly, a recent analysis of two separate registries (56) revealed that patients diagnosed with idiopathic PAH displaying a lung phenotype (57), typically older males who smoked a lot and have very low carbon monoxide diffusing capacity (DL_{CO}) and patients diagnosed with severe PH associated with chronic lung disease demonstrated similar survival rates, distinct from classical idiopathic PAH phenotype patients (58). Notably, both groups exhibited comparable characteristics in terms of age,

smoking history, DL_{CO}, and pulmonary hemodynamics, differing only in the severity of airflow obstruction. The forced expiratory volume in the first second (FEV_1) was 59%predicted in those diagnosed with severe PH associated with chronic lung disease and 71%predicted in those diagnosed with idiopathic PAH with a lung phenotype. This suggests that both groups encompass patients with remarkably similar clinical profiles but different diagnoses. This distinction bears significance for treatment, as clinical guidelines recommend PAH therapy for patients diagnosed with idiopathic PAH with chronic lung disease as a comorbidity (group 1 of PH classification). However, if diagnosed with PH associated with COPD (group 3 of PH classification), PAH therapies are generally not recommended in non-severe PH associated with chronic lung disease, but may be considered in experts centres in cases with severe PH (as defined by PVR ≥5 wood units) (6). To ascertain whether severe PH associated with lung disease constitutes a distinct pulmonary vasculopathy, understanding whether this phenotype is related to some specific characteristics is crucial.

Cardiac comorbidities are also common in patients with respiratory diseases, especially in COPD, and can also contribute to PH. Heart failure frequently correlates with pulmonary hypertension (PH). Among patients with HFpEF, the incidence of PH varies from 20% to 100% depending on diverse definitions and diagnostic methodologies (59). Furthermore, in individuals with advanced COPD and those experiencing acute exacerbations, the coexistence of PH and left heart failure is prevalent in the majority of cases (59).

The primary predisposing factor for PH onset in the broader population is left heart disease, encompassing both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), a well-established comorbidity observed in individuals with COPD (60) or ILD. The literature have shown a significant proportion of patients meeting echo-based criteria indicative of possible or probable PH also exhibited manifestations of left heart failure (60). Notably, HFpEF has been discernible across all patients with confirmed PH via right heart catheterization (RHC). These findings underscore the predominant role of left

heart failure in precipitating PH among patients with respiratory diseases and offer insights into the presence of severe PH in some patients (60).

Conclusion

In conclusion, the relationship between pulmonary vascular diseases and chronic lung diseases can involve both cause and consequence dynamics. While certain factors, such as altered expression of mediators and growth factors, may contribute to the development of both conditions, the exact causal pathways and temporal sequence of events are complex and multifactorial. For example, pulmonary vascular remodelling and endothelial dysfunction observed in chronic lung diseases may contribute to the development of pulmonary hypertension (PH), suggesting a consequential relationship. However, factors such as hypoxia and inflammation, which are characteristic of chronic lung diseases, can also directly contribute to the development of pulmonary vascular diseases, indicating a causative role. Overall, the cause-and-consequence relationship between pulmonary vascular diseases and chronic lung diseases is likely bidirectional and context-dependent, influenced by various genetic, environmental, and physiological factors.

Key points

- Shared pathogenic mechanisms between PAH and Group 3 PH, including altered expression of mediators and growth factors implicated in both conditions.
- Factors such as hypoxia, hypoxemia, and hypercapnia contribute to pulmonary vascular remodeling and endothelial dysfunction in chronic lung disease, yet the exclusive role of hypoxia in PH in these diseases, especially in COPD, is being

reassessed, with emerging evidence pointing towards cigarette smoke products potentially initiating pulmonary vascular impairment.

- Understanding the complex interaction among pulmonary vascular, parenchymal, and airway compartments is essential for advancing diagnostic and therapeutic methods

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Conflicts of interest

All other authors have nothing to disclose.

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Figure legends

Figure 1. Mechanisms involved in pulmonary hypertension in chronic lung diseases