REVIEW

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Pathophysiology of Pulmonary Hypertension in Chronic Parenchymal Lung Disease

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ABSTRACT

Pulmonary hypertension commonly complicates chronic obstructive pulmonary disease and interstitial lung disease. The association of chronic lung disease and pulmonary hypertension portends a worse prognosis. The pathophysiology of pulmonary hypertension differs in the presence or absence of lung disease. We describe the physiological determinants of the normal pulmonary circulation to better understand the pathophysiological factors implicated in chronic parenchymal lung disease–associated pulmonary hypertension. This review will focus on the pathophysiology of 3 forms of chronic lung disease-associated pulmonary hypertension: idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and sarcoidosis.
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KEYWORDS: Chronic obstructive pulmonary disease; Idiopathic pulmonary fibrosis; Pulmonary fibrosis; Pulmonary hypertension; Sarcoidosis

Chronic obstructive pulmonary disease and interstitial lung diseases are associated commonly with pulmonary hypertension. The current consensus definition for pulmonary hypertension in chronic respiratory disease is:

1. Chronic lung disease with pulmonary hypertension when mean pulmonary arterial pressure is ≥25 mm Hg
2. Chronic lung disease with severe pulmonary hypertension when the mean pulmonary arterial pressure is ≥35 mm Hg or ≥25 but ≤35 mm Hg with low cardiac index (<2 L/min/m^2).[1]

The prevalence of pulmonary hypertension in chronic lung disease varies widely depending on the diagnostic method, the definition of pulmonary hypertension used, and the patient population studied.[2-11] Patients with chronic lung disease–associated pulmonary hypertension have a significantly worse prognosis than patients without pulmonary hypertension.[2,4,6,12,13] This review will focus on the pathophysiology of 3 forms of chronic lung disease-associated pulmonary hypertension: idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and sarcoidosis.

Nearly the entire cardiac output normally flows through the pulmonary circuit. Despite this, the pulmonary vascular pressure and resistance are much less than the systemic circulation. This is because the pulmonary circulation adapts to large changes in cardiac output by distending or recruiting previously underperfused pulmonary capillaries. Thus, pulmonary vascular resistance decreases as pulmonary blood flow increases. Pulmonary vascular resistance is expressed as follows:

$$\text{Pulmonary vascular resistance} = \frac{\text{Pulmonary driving pressure}}{\text{cardiac output}}$$

Unlike the systemic circulation with its greater vasomotor activity, the pulmonary circulation has limited ability to control regional pulmonary blood flow and is influenced greatly by various other active and passive factors (**Tables 1** and **2**). The pulmonary arteries and arterioles with their muscular walls are mainly

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extra-alveolar and regulate pulmonary vascular resistance via active nervous, humoral, or gaseous mechanisms. In contrast, the pulmonary capillaries lie adjacent to alveolar walls; therefore, the resistance of these alveolar vessels is influenced greatly by alveolar pressure and volume. Thus, in the normal pulmonary circulation, vessels devoid of active vasoconstriction play a pivotal role in regulating pulmonary vascular resistance and distributing pulmonary blood flow.[14]

Hypoxic pulmonary vasoconstriction also plays a major role in the active regulation of pulmonary vascular resistance and pulmonary blood flow. This regional reflexive mechanism is an adaptive response to divert pulmonary blood flow away from regions of low oxygen tension and plays an integral part in optimizing ventilation/perfusion matching. Reflexive hypoxic pulmonary vasoconstriction has multiple mechanisms resulting from the direct effects of hypoxia on pulmonary vascular smooth muscle cells,[15-17] impaired release of endothelium-derived vasodilators such as nitric oxide and prostaglandin,[18] and increased expression of the vasoconstrictive peptide, endothelin.[19,20]

CLINICAL SIGNIFICANCE

- Regulation of blood flow in the normal pulmonary circulation occurs at the level of the pulmonary capillaries.
- In patients with chronic parenchymal lung disease, pulmonary hypertension carries a worse prognosis.
- Chronic parenchymal lung disease–associated pulmonary hypertension is the result of interactions among mechanical factors, reflexive hypoxic pulmonary vasoconstriction, and pulmonary vascular remodeling.
- The heterogeneous mechanism of pulmonary hypertension occurrence in chronic parenchymal lung disease complicates the use of pulmonary vasodilators therapy.

Various pathophysiological pathways account for the development of pulmonary hypertension in patients with chronic lung disease. Normally, the thin wall of the pulmonary arteries and arterioles and the nonmuscularized pulmonary capillaries allow the vessels to distend rather than actively constrict or dilate.[21] In pulmonary hypertension, pulmonary vascular remodeling thickens the arterial wall and increases resistance by reducing the luminal diameter. This reduces the ability of the vessel to distend passively and potentiates the further increase in pulmonary vascular resistance produced by active vasoconstriction.[22,23]

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In patients with chronic obstructive pulmonary disease, the elevation in pulmonary vascular resistance is the result of a complex interaction among mechanical factors, reflexive hypoxic pulmonary vasoconstriction, and pulmonary vascular remodeling (**Table 3**). In chronic bronchitis, expiratory airflow limitation increases alveolar air volume, resulting in dynamic hyperinflation. As the alveoli expands, the adjacent intra-alveolar pulmonary capillaries are stretched and their diameter decreases. The resistance to pulmonary blood flow increases greatly as the intra-alveolar pressure increases because the adjacent vessels become longer (resistance is directly proportional to length) and their radii become smaller (resistance is inversely proportional to radius to the fourth power). In addition, overexpansion of the alveoli also may directly compress these capillaries, further contributing to the increase in pulmonary vascular resistance.[24]

Contrary to prior beliefs, emphysematous destruction of the pulmonary vascular bed plays a less significant role in the development of pulmonary hypertension among patients with chronic obstructive pulmonary disease. In patients with chronic obstructive pulmonary disease, there is no significant correlation between the pulmonary arterial pressure or resistance and the extent of emphysema as measured by computed tomography lung density.[25] The obliteration of alveolar vessels that is seen in emphysema is associated typically with normal resting pulmonary arterial pressure until the very late stages, when pulmonary vascular destruction leads to severe diffusion limitation with resting arterial hypoxemia. However, loss of pulmonary vascular bed does contribute to the increase in pulmonary vascular resistance during exercise in such patients because of the inability to recruit or distend underperfused vessels.[26]

The lack of reversibility in response to oxygen therapy or nitric oxide inhalation suggests that a more chronic structural change rather than the acute hypoxic pulmonary vasoconstriction mechanism accounts for pulmonary hypertension development in patients with chronic obstructive pulmonary disease.[27-31] This process of pulmonary vascular remodeling involves mainly the small pulmonary arteries and is characterized by neomuscularization, intimal thickening, and medial hypertrophy.[23] Many pathophysiological mechanisms have been implicated in pulmonary vascular remodeling among patients with chronic obstructive pulmonary disease and pulmonary hypertension. These include chronic hypoxia, cigarette smoking injury,[32-35] and airway and vascular wall inflammation.[36,37] All of these factors lead to vascular endothelial damage and subsequent structural changes within the vascular wall. Chronic hypoxia contributes to pulmonary vascular remodeling through production of hypoxia-induced mitogenic factor and interleukin-6, both of which promote vascular endothelial cell proliferation.[38,39] Recently, increased expression of adenosine A2B receptor and hyaluronan has been implicated.[40] Recent studies have demonstrated that patients with chronic obstructive pulmonary disease with LL-genotype of serotonin, a potent stimulator of