Opinion

Pathology

Pulmonary Hypertension
What Are the Underlying Mechanisms?

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Pulmonary hypertension is a multifaceted condition defined by elevated blood pressure within the pulmonary arteries, which may result in significant injury and stress on the heart. The fundamental mechanisms underlying pulmonary hypertension are complex and encompass a range of factors, including vasoconstriction, vascular remodeling, inflammation, and endothelial dysfunction. Vasoconstriction transpires when the smooth muscle cells within the pulmonary arteries undergo abnormal contraction, resulting in the constriction of the blood vessels and a subsequent limitation of blood flow. Vascular remodeling pertains to the structural alterations occurring within the vessel walls, encompassing thickening and stiffening, which may subsequently lead to increased pressure levels. Inflammation serves a pivotal function in initiating immune responses that can result in the deterioration of arterial walls. Endothelial dysfunction refers to the compromised functionality of the endothelium that lines the blood vessels, which adversely impacts their capacity to modulate blood flow and pressure. These fundamental mechanisms frequently operate concurrently to intensify pulmonary hypertension, underscoring the necessity of addressing multiple pathways in its therapeutic management.

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PULMONARY hypertension (PH) is a grave and potentially life-threatening condition distinguished by elevated blood pressure within the pulmonary arteries (Rosenblum, 2024). If left untreated, it may result in cardiac failure and other complications. Understanding the underlying mechanisms of PH is crucial in devising effective treatments and improving outcomes for patients (McLaughlin & McGoon, 2006).

A fundamental underlying mechanism of PH is vascular remodeling (Humbert et al., 2018). In PH, the walls of the pulmonary arteries become thickened and stiff, restricting the blood

vessels and increasing the resistance to blood flow (Sun & Chan, 2018). This remodeling process is induced by the aberrant proliferation of smooth muscle cells and endothelial dysfunction, leading to vascular constriction and diminished blood flow to the lungs.

Another significant mechanism contributing to the pathogenesis of PH is inflammation (Wang & Chesler, 2011). Chronic inflammation within the pulmonary system can result in damage to the pulmonary vascular endothelium, thereby compromising its capacity to modulate blood flow and facilitate vasodilation (Budhiraja et al., 2004; Kotlyarov, 2022) (Sun et al., 2023). This inflammatory response may be elicited by a multitude of factors, including infections, autoimmune disorders, or exposure to contaminants and pollutants.

Endothelial dysfunction is likewise a prevalent characteristic of pulmonary hypertension (Cheng & Zhang, 2024). The endothelium constitutes a delicate layer of cells that lines the interior of blood vessels and is instrumental in the regulation of vascular tone and the coagulation of blood (Liotti et al., 2023). In PH, the endothelium becomes dysfunctional, leading to increased vasoconstriction, thrombosis, and impaired nitric oxide production, which is a potent vasodilator.

An additional mechanism contributing to PH is the dysregulation of the renin-angiotensin-aldosterone system (RAAS) (Ali et al., 2018; Patel & Mitsnefes, 2024). This hormonal system is accountable for the regulation of blood pressure and the maintenance of fluid equilibrium within the body. In PH, there exists an overactivation of the RAAS, resulting in heightened vasoconstriction, sodium retention, and fluid accumulation (Gómez, 2021; Patel et al., 2017). These factors may further aggravate pulmonary vascular remodeling and dysfunction.

Hypoxia also serves as a contributing factor in the pathogenesis of pulmonary hypertension (Tuder et al., 2013). Prolonged exposure to diminished oxygen levels, as encountered in high-altitude environments or in individuals suffering from pulmonary conditions such as Chronic Obstructive Pulmonary Disease (COPD), may induce pulmonary vasoconstriction and vascular remodeling (Garcia et al., 2022; Kotlyarov, 2022). Hypoxia-induced changes in gene expression and signaling pathways can further promote the development of PH.

Hormonal imbalances can also be a contributing factor to PH. Dysregulations in hormones, including estrogen and thyroid hormones, can adversely impact the functionality of blood vessels and the heart, resulting in elevated pressure within the pulmonary arteries (Austin et al., 2013). Hormonal changes that occur during pregnancy or menopause may also increase the risk of developing PH.

Obesity and metabolic syndrome are additional risk factors for PH (Hung, 2024). Excess body weight can impose significant stress on the heart and lungs, resulting in elevated pressure within the pulmonary arteries (Friedman & Andrus, 2012). Metabolic syndrome, which is characterized by a combination of high blood pressure, elevated cholesterol, and insulin resistance, can also contribute to the development of PH (Lang & Palazzini, 2019).

Infectious diseases such as HIV or schistosomiasis can also contribute to the development of PH (Ryu et al., 2007). These infections have the potential to inflict harm on the lungs and blood vessels, resulting in elevated pressure within the pulmonary arteries (Souza et al., 2009; Petrosillo, 2010). Treating the underlying infection may help to alleviate PH symptoms in some cases.

Certain medications or recreational substances can also contribute to the development of PH (Naeije & Barberá, 2001). Substances such as methamphetamines, cocaine, and certain weight loss medications have the potential to elevate blood pressure and impose additional stress on the heart and airways, which may result in PH (Fares & Bazán, 2015; Girgis & Mathai, 2007). It is crucial to carefully monitor medications and avoid recreational drugs to reduce the risk of developing PH.

Irregularities in the synthesis and signaling of prostacyclin, an additional vasodilator, may contribute to the onset of PH (Gomberg‐Maitland & Olschewski, 2008; Krug, 2009). Prostacyclin is synthesized by the endothelium, facilitating vasodilation and inhibiting platelet aggregation (Stitham et al., 2011). Interruption of the prostacyclin signaling pathway may result in heightened vasoconstriction and elevated blood pressure in the pulmonary arteries.

Genetic factors also contribute to the etiology of PH (Tuder et al., 1999). Mutations in genes encoding proteins implicated in vascular smooth muscle cell proliferation, endothelial function, or ion channel regulation can predispose individuals to PH (Soubrier et al., 2013). These genetic modifications have the potential to disturb the normal homeostasis of the pulmonary vasculature and may play a significant role in the pathogenesis of the disease.

In addition to these mechanisms, oxidative stress and mitochondrial dysfunction have been associated with the pathogenesis of PH (Dorfmüller et al., 2011; Lai et al., 2014). Elevated production of reactive oxygen species can result in oxidative injury to the vascular endothelium and smooth muscle cells, subsequently inducing inflammation, apoptosis, and vascular remodeling (Plecitá‐Hlavatá et al., 2017). Mitochondrial dysfunction can impair cellular energy production and contribute to pulmonary vascular dysfunction in PH.

In sum, PH is a multifaceted and intricate condition characterized by a variety of underlying mechanisms that contribute to its pathogenesis. Understanding these mechanisms is crucial for developing targeted therapies that can effectively alleviate symptoms, slow disease progression, and enhance outcomes for patients with PH. Additional investigation into the molecular and cellular mechanisms underlying PH is essential to identify novel therapeutic targets and enhance the management of this debilitating condition.■

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