Literature Review

Pulmonary Hypertension: Understanding the Underlying Anatomy and Physiology of Pulmonary Circulation

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Abstract

The circulatory system has a vital role in fulfilling oxygen demand in tissues and maintaining homeostasis. There are two types of circulatory systems in our body, the systemic and pulmonary circulation. Pulmonary circulation, the critical pathway of blood oxygenation through heart-lung-pulmonary vascular interaction, remains poorly understood despite its central role in the various pulmonary vascular diseases. One of the most prevalent pulmonary vascular diseases is pulmonary hypertension (PH), which is characterized by high mortality and disease progression. A thorough understanding of the physiologic structure and function of pulmonary circulation is essential for diagnosing and treating patients with PH. Pulmonary blood flow is determined by pulmonary vascular pressure (PVP) and pulmonary vascular resistance (PVR). Lung volume, neural factors (sympathetic and parasympathetic nervous systems), humoral factors (vasoconstrictor and vasodilator), and alveolar hypoxia play an important role in regulating PVR. Alveolar hypoxia triggers hypoxic pulmonary vasoconstriction to maintain the ventilation-perfusion ratio balance. High PVR increases pulmonary arterial pressure (P_a), which is the main pathophysiology of PH. In addition, endothelial dysfunction and vasoactive imbalance also contribute significantly to the pathogenesis of the disease.

Keywords: hypoxic pulmonary vasoconstriction, pulmonary circulation, pulmonary hypertension, pulmonary vascular resistance

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INTRODUCTION

The circulatory system is an important component in maintaining the human body's homeostasis. Blood vessels distribute blood from the heart to tissues in many parts of the body to fulfil their oxygen demands. Basically, the human circulatory system is divided into two parts: the systemic and pulmonary circulation.[1,2] Systemic circulation brings blood from the heart to all organs and tissues, excluding the lungs, while pulmonary circulation brings blood from the heart to the lungs and vice versa. Besides the lungs, pulmonary blood vessels are also important parts of pulmonary circulation.[3,4]

There are several known pulmonary vascular diseases, including pulmonary vasculitis, pulmonary arteriovenous malformation (PAVM), pulmonary vascular malignancy, pulmonary thromboembolism (PE), and pulmonary hypertension (PH).[5] The incidence of these diseases varies widely depending on the type. For example, pulmonary vasculitis, PAVM, and pulmonary vascular malignancy are relatively rare, with incidences of 12.8–30.1 per 1 million population, 0.001–0.03%, and 1 per 2,600 population, respectively.[6–8] The incidence of PE has been estimated to range from 0.039 to 1.15 per 1,000 population.[9–11]

On the other hand, PH affects about 1% of the global population, making it the most common pulmonary vascular disorder. It has high morbidity and mortality, especially without early and proper treatment.[9–11] A good and comprehensive understanding of the structure and physiology of pulmonary circulation is crucial to diagnose and treat patients with PH.

PULMONARY HYPERTENSION

Pulmonary hypertension was initially recognized as a clinical syndrome and was not defined using objective parameters such as mean pulmonary arterial pressure (mPAP). The definition of

PH keeps changing from time to time. Currently, PH is defined as an increase of mPAP more than 20-25 mmHg, measured objectively by right heart catheterization (RHC) during rest.[11,12] In Britain, the estimated incidence rate of PH was 97-125 cases per 1 million population.[12] This disease is more commonly found in women (54.5%) and individuals aged >65 years.[2,10] However, the true incidence and epidemiological data of PH in South East Asia are still scarce, especially in Indonesia.[14,15]

There are five main classifications of PH based on the etiology: pulmonary arterial hypertension (Group 1), pulmonary hypertension caused by left heart disease (Group 2), pulmonary hypertension caused by pulmonary diseases and/or hypoxia (Group 3), chronic thromboembolic pulmonary hypertension (Group 4), pulmonary hypertension with unclear and/or multi-factorial underlying mechanism (Group 5). Groups 2, 3, and 4 are the most common etiologies.[16] Blanco et al found that 90% of end-stage chronic obstructive pulmonary disease (COPD) patients had elevated mPAP (average 20-35 mmHg).[17] Nathan et al also found increased mPAP >25 mmHg in 30-50% of Idiopathic Pulmonary Fibrosis (IPF) patients.[18]

Patients with PH often present with subtle and non-specific symptoms: exertional dyspnea, fatigue, chest discomfort or pain, dizziness, and palpitations.[19,20] Usually, the patients start to show more obvious clinical manifestations when they have developed right heart failure.[12] In addition, certain populations are at higher risk of developing PH due to the underlying conditions, such as older age (>65 years old), chronic lung diseases (including tuberculosis), cardiac diseases, and autoimmune disorders.[10,21–24]

There are several diagnostic methods to confirm if a patient has PH or not. The gold standard for diagnosing PH is RHC, which directly measures mPAP. Echocardiography can also be used to estimate mPAP and assess right ventricular function non-invasively. Chest computerized tomography (CT) scan and pulmonary function test are essential for evaluating the structural and functional condition of the lungs. In addition, cardiopulmonary exercise testing (CPET) also provides additional data to quantify exercise capacity and the grade of disease severity.[11,20]

In general, the mean survival rate of PH is 2.8 years.[9,10] Analysis on Pulmonary Hypertension Association Registry (PHAR) by Chang et al showed that mortality rates of PH patients in the first, second, and third year were 8%, 16%, and 21%, respectively. High-risk PH patients face worse outcomes, with 3-year mortality reaching 55%.[25] In addition, despite therapeutic advances, the survival rate has not significantly improved over time, particularly in populations aged >56 years.[26] Therefore, early diagnosis and adequate therapy are essential, as initial combination treatment has been shown to improve the 1-year survival rate with an adjusted hazard ratio of 0.43 (95% CI=0.19-0.95).[25]

PULMONARY CIRCULATION ESSENTIAL ANATOMY

Pulmonary circulation is defined as the movement of blood from the heart to the lungs and vice versa.[4,27] The main components of pulmonary circulation are the pulmonary artery, pulmonary vein, pulmonary capillary network, heart, and lungs.[3,28] Pulmonary circulation contains approximately 250-300 mL/m^2 body surface area and about 60-70 mL/m^2 located in the pulmonary capillary network.[4]

Low-oxygen blood from systemic circulation enters the right atrium, then moves to the right ventricle through the tricuspid valve. The right ventricle then pumps blood through the pulmonary semilunar valve to the pulmonary trunk, the right and left pulmonary artery, and finally to both lungs. Gas diffusion occurs in the pulmonary capillary network, alveoli, and pulmonary veins. This process produces oxygenated blood, which then flows through the pulmonary vein to the left atrium and then to the left ventricle to be distributed to systemic circulation.[27,28]

Pulmonary Artery

In general, adults have three types of pulmonary arteries: elastic arteries, muscular arteries, and pulmonary arterioles. Elastic arteries, including the pulmonary trunk and all extralobular

pulmonary arteries, have an external diameter of >1,000 µm, while muscular arteries have an external diameter of 100-1,000 µm.[3,29]On the other hand, pulmonary arterioles, the terminal branch of pulmonary arteries, have an external diameter of <100 µm.[2] The main pulmonary artery, commonly known as the pulmonary trunk, starts from the right ventricle and extends to the posterosuperior side of the aorta, then divides into the primary branches (right and left pulmonary artery) as depicted in Figure 1.[3,29]

Both right and left pulmonary arteries further branch into lobar arteries (secondary branches), segmental arteries (tertiary branches), and finally the subsegmental arteries (in parallel with bronchial segments).[2,3,16] Pulmonary arteries are commonly located in the dorsolateral side of the bronchi and have many variations in both segmental and subsegmental levels. Pulmonary arteries culminate at the hilum together with the main bronchus and pulmonary veins.[28]

The right pulmonary artery runs horizontally through the posterior side of the ascending aorta and superior vena cava. It is estimated that 75% of this artery is located inside the pericardial cavity. This artery has two main branches, the superior branch (anterior trunk), which provides blood supply to the superior lobe of the right lung, and the inferior branch, which supplies blood to the anterior part of the medial lobe and the upper part of the inferior lobe.[2,28]

The left pulmonary artery exits the pericardium through the lower side of the aortic arch (ligamentum arteriosum), proceeds to the anterior side of the aortic arch, and enters the oblique fissure. This artery then arches behind the left main bronchus, encircling approximately three-quarters of the superior lobe of the left lung's bronchial circumference. There are many variations of the left pulmonary artery branches. The apical anterior branch supplies blood to the apical-posterior and anterior segments of the left lung's superior lobe. A single segmental artery in the basal part branches into two arteries and supplies blood to the anteromedial, posterior, and lateral-basal segments of the left lung.[28]

From a histological perspective, pulmonary arteries have three distinct layers: tunica adventitia, tunica media, and tunica intima (Figure 2). The adventitial layer consists of extracellular matrix such as fibrins, mast cells, fibroblasts, elastin, and collagen. The tunica media has few smooth muscles and elastic lamina. The innermost layer, tunica intima, comprises a single layer of endothelial cells surrounding the arterial lumen.[16,27]

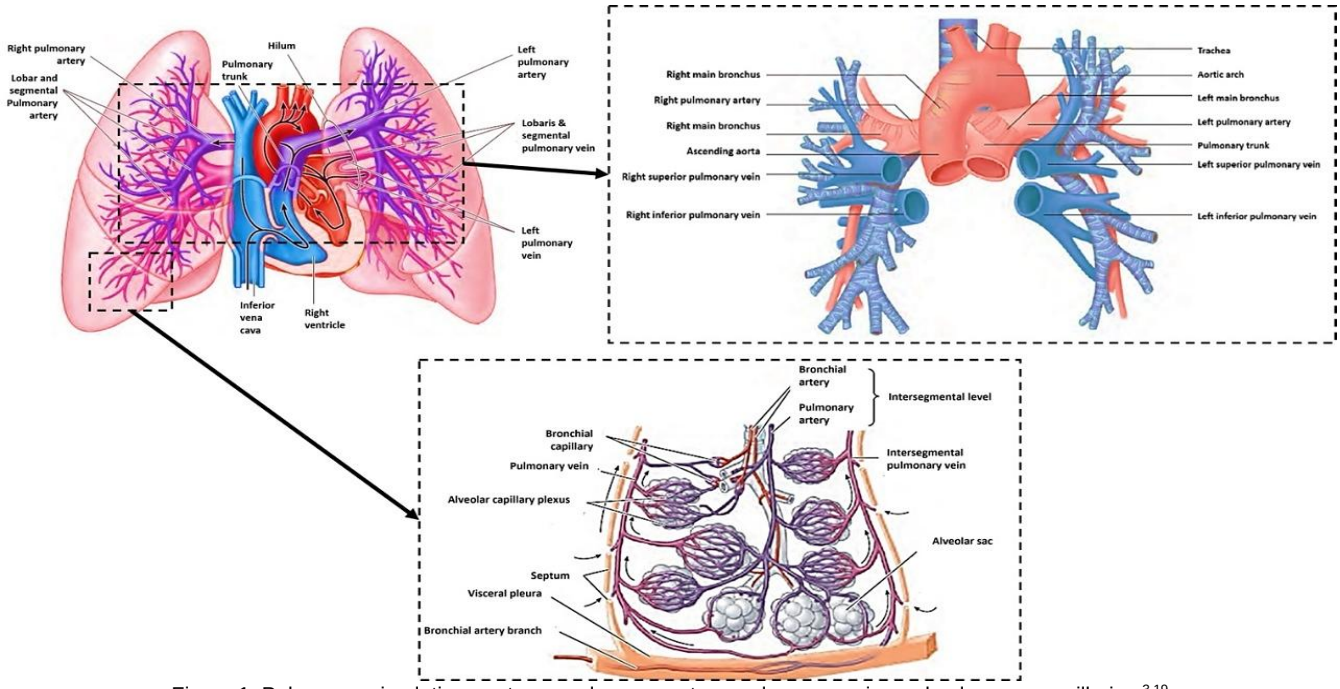


Figure 1. Pulmonary circulation anatomy: pulmonary artery, pulmonary vein, and pulmonary capillaries.[3,19]

The main role of this layer is to optimize gas exchange, regulate vascular tone, and maintain the integrity of blood vessel walls.[16,27] The thin wall and small amount of smooth muscle provide elastic properties to the pulmonary artery.[4,30]

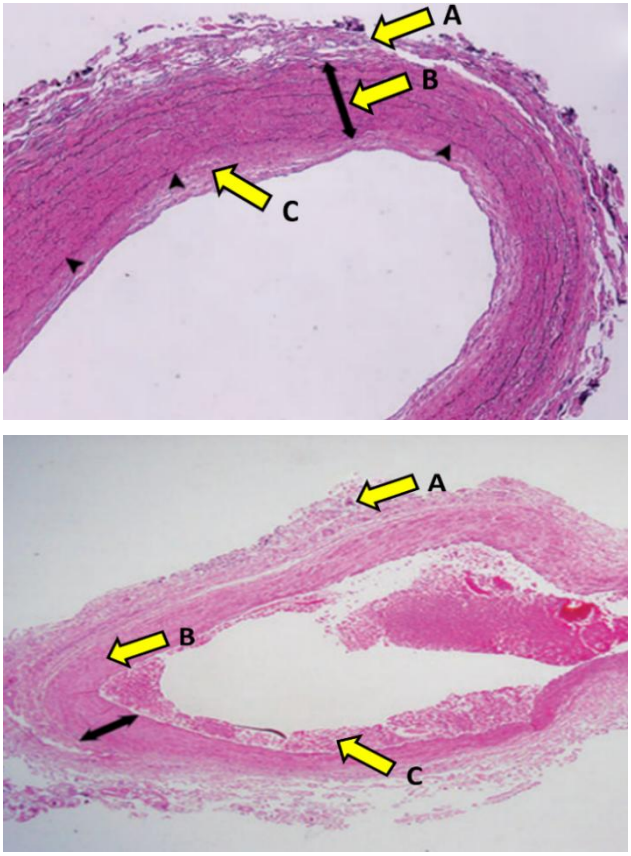


Figure 2. Histology of the pulmonary artery (left) and pulmonary vein (right) visualized by H&E staining. Each has three main layers: (A) tunica adventitia, (B) tunica media, and (C) tunica intima.[19]

Pulmonary Vein

There are four pulmonary veins in total: the superior and inferior pulmonary veins for each lung. Small intrasegmental and intersegmental veins form one trunk from each lobe, three veins for the right lung, and two veins for the left lung. Blood from the alveolar capillary is brought to the left atrium and then distributed to the systemic circulation via the left ventricle. Then, pulmonary veins penetrate the fibrous pericardium to the posterosuperior part of the left atrium. Then, pulmonary veins enter the mediastinum on the anteroinferior side of the pulmonary artery.[28,31]

The right pulmonary vein branches into the right superior and inferior pulmonary veins. The right superior pulmonary vein supplies the upper and medial lobe of the right lung, while the right inferior pulmonary vein supplies the inferior lobe of the right lung. In addition, the left pulmonary vein also branches into two segments: the superior branch, supplying the upper lobe of the left lung, and the inferior branch, supplying the inferior lobe of the left lung. Both of these left veins are located on the anterior side of the descending aorta.[3]

From a histological perspective, like pulmonary arteries, pulmonary veins also have three main layers, as depicted in Figure 2. However, the main distinction between these two vessels is that pulmonary veins have a thinner tunica media and a thicker tunica adventitia compared to pulmonary arteries.[30]

Pulmonary Capillary Network

The pulmonary artery tree branches down to the capillary level and forms a thick mesh on the epithelial wall, septum, and alveolar sac (Figure 1). There are 280 billion capillary anastomoses for 300 million alveoli in the lungs, each measuring 6 µm in diameter. The high number of capillaries plays an important role in increasing the surface area for diffusion to facilitate efficient gas exchange.[2,27,32] These capillaries have very slender walls with a small amount of smooth muscle, thus making them very elastic and resulting in low vascular resistance.[4,16,32] Additionally, although pulmonary capillaries have the smallest diameter, they have the largest surface area compared to other blood vessels in the pulmonary circulation (Table 1).[31]

Table 1. Comparison of each blood vessel in the pulmonary circulation[31]

Vessel	Diameter (µm)	Surface area (m^2)	Blood volume (mL)
Artery	>500	0.4	68
Arteriole	13-500	1.0	18
Capillary	10	50-70	60-200
Venule	13-500	1.2	13
Vein	>500	0,1	58

PULMONARY CIRCULATION ESSENTIAL PHYSIOLOGY

Pulmonary Vascular Pressure

Unlike the blood vessels in systemic circulation, the average pressure in pulmonary blood

vessels is always low under normal conditions. This is due to the thin capillary wall and small amount of smooth muscle, which results in low pulmonary vascular pressure (PVP). In pulmonary circulation, as the lungs only need to receive blood from the cardiac output, the low pulmonary artery pressure is sufficient to pump blood from the heart to the lungs.[4,33]

Pulmonary Vascular Resistance

Pulmonary vascular resistance (PVR) is the resistance of pulmonary arteries to blood flow from the left atrium and is influenced by both pressure and volume.[4,33,34] Because PVR cannot be directly measured, it has to be calculated indirectly using Poiseuille's law. Poiseuille's law states that in a Newtonian fluid flowing constantly through a rigid tube, the difference between input pressure (P_I) and output pressure (P_O) equals flow velocity (Q) multiplied by resistance (R). Both P_I and P_O can be measured via right heart catheterization.[35,36]

Transmural pressure plays a key role in maintaining PVR. Transmural pressure is defined as the difference between alveolar pressure (P_A) and intrathoracic pressure. Under physiological conditions, P_A is always higher than the pressure in interstitial tissue.[4] This pressure determines whether pulmonary blood vessels undergo distention or recruitment based on their diameter. If the pressure inside a pulmonary blood vessel is higher than that of its surroundings, vasodilation occurs, thus decreasing PVR. In contrast, if the pressure inside pulmonary blood vessels is lower, vasoconstriction occurs, and PVR. The negative pressure within pulmonary blood vessels will collapse of the diameter.[4,35,36]

An increase in pulmonary artery pressure (P_a) and pulmonary vein pressure (P_v) can also boost PVR. As previously mentioned, the human body compensates for such events through the recruitment and distention mechanism (Figure 3).[4,37] Recruitment refers to the opening of the previously occluded blood vessels. If P_a increases, cardiac output also rises without a proportional escalation in average mPAP. Under this condition, when P_a finally reaches the critical opening pressure, occluded vessels open to allow blood flow, reducing PVR, enhancing diffusion surface area, and finally reducing alveolar dead space.[4,34–36] Distention occurs when there is an increase in blood volume. During elevated P_a levels, pulmonary blood vessels distend and change their shape from flat to circular. Although both recruitment and distention occur simultaneously, distention typically only happens when P_a is significantly elevated.[4,36]

In addition to pressure changes, lung volume also plays a role in determining PVR values. When lung volume is very small (approaching residual volume) or very large (approaching total lung capacity), PVR reaches its peak. In contrast, the lowest PVR occurs at the end of normal expiration (functional residual capacity). To understand this concept, pulmonary blood vessels need to be classified into intra-alveolar and extra-alveolar vessels.[4,34]

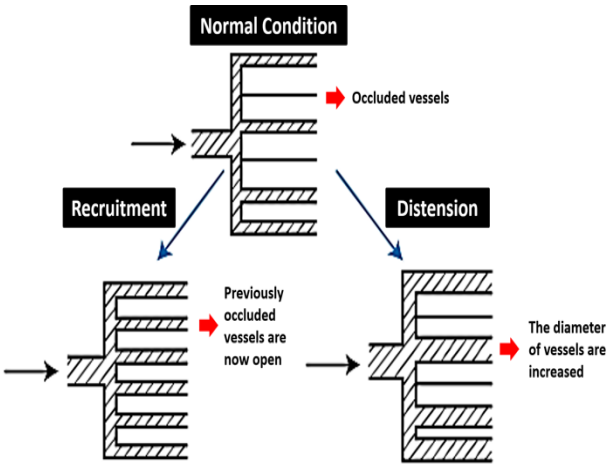


Figure 3. Recruitment and distention as a compensation mechanism to maintain low PVR when P_a is elevated[33]

During normal inspiration, pulmonary blood vessels distend due to the traction of lung parenchyma, resulting in low PVR. In contrast, during normal expiration, the elastic tissue and smooth muscle in the vessel wall withhold the distention of blood vessels, thus maintaining low PVR.[4,36]

During deep inspiration, intra-alveolar pressure and alveolar volume increase. This causes the capillaries surrounding the alveoli to distend drastically, reducing the diameter and increasing their length. It is important to note that resistance is directly proportional to distance and inversely proportional to

diameter. Therefore, the PVR of intra-alveolar vessels increases. In contrast, during maximal expiration, the low lung volume opens the capillaries, thus lowering the PVR.[4,33]

Parts of extra-alveolar vessels are exposed to intrapleural pressure.[36] At low lung volume, the intrapleural pressure becomes more positive, compressing the alveoli, decreasing radial traction, and finally drastically elevating PVR. In contrast, when lung volume approaches total lung capacity, intrapleural pressure becomes negative, resulting in increased radial traction and capillary distention, thus lowering PVR.[4,33,36]

Regulation of Pulmonary Circulation

The blood flow of the lung is determined by the vascular smooth muscle tone. High smooth muscle tone will increase PVR, while low smooth muscle tone decreases it. While lung volume, pulmonary blood pressure, alveolar pressure, interstitial pressure, gravity, and body position passively regulate the vascular smooth muscle tone, active regulation is determined by neural and humoral factors.[4,34]

Like other vessels in the human body, pulmonary vasculature is also innervated by sympathetic and parasympathetic nerves. These nerves are primarily found in vessels with a diameter greater than 30 µm. The activation of the sympathetic nervous system decreases vascular distensibility, resulting in higher PVR. In contrast, stimulation of parasympathetic nerves induces vasodilation, thus reducing PVR.[34,35]

Humoral factors also play roles in regulating PVR. Substances such as histamine, catecholamine, prostaglandin $E_{2\text{-}\alpha}$ ($PGE_{2\text{-}\alpha}$), prostaglandin E_2 (PGE_2), thromboxane (TXA), and endothelin (ET) are classified as vasoactive substances that can trigger vasoconstriction. On the other hand, substances such as acetylcholine, β_2-adrenergic-agonist, nitric oxide (NO), prostaglandin E_1 (PGE_1), prostacyclin (PGI_2), and bradykinin induce vasodilatation.[34,35] Furthermore, prolonged alveolar hypoxia can also induce vasoconstriction through a mechanism commonly known as hypoxic pulmonary vasoconstriction.[38,39]

Hypoxic Pulmonary Vasoconstriction

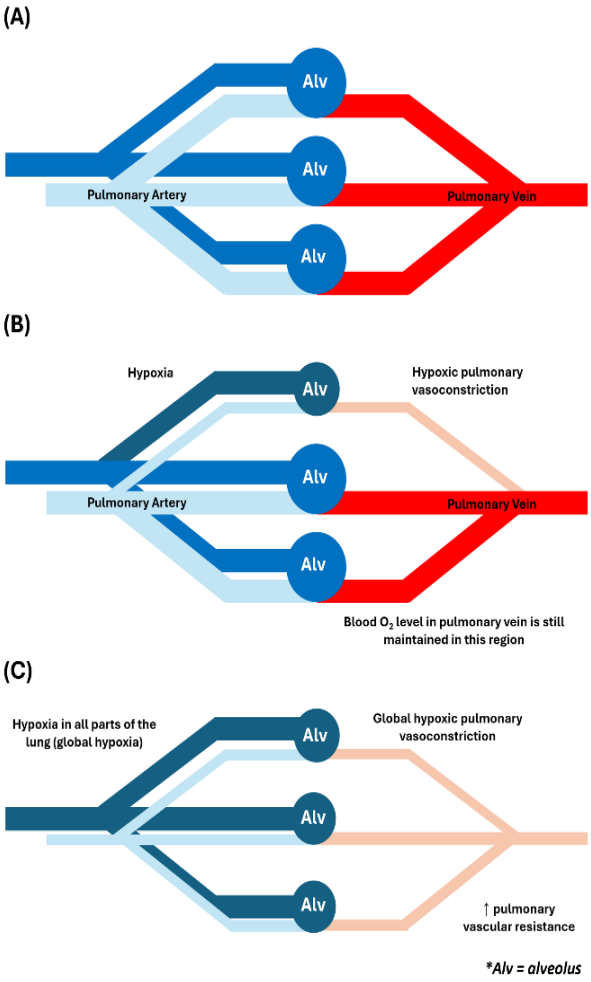


Figure 4. Illustration of the pulmonary circulation during normal blood O_2 levels (A). Regional hypoxic pulmonary vasoconstriction due to hypoxia in one part of the lung (B). Global hypoxic pulmonary vasoconstriction because of hypoxia that occurs in almost all regions of the lung (C).[39]

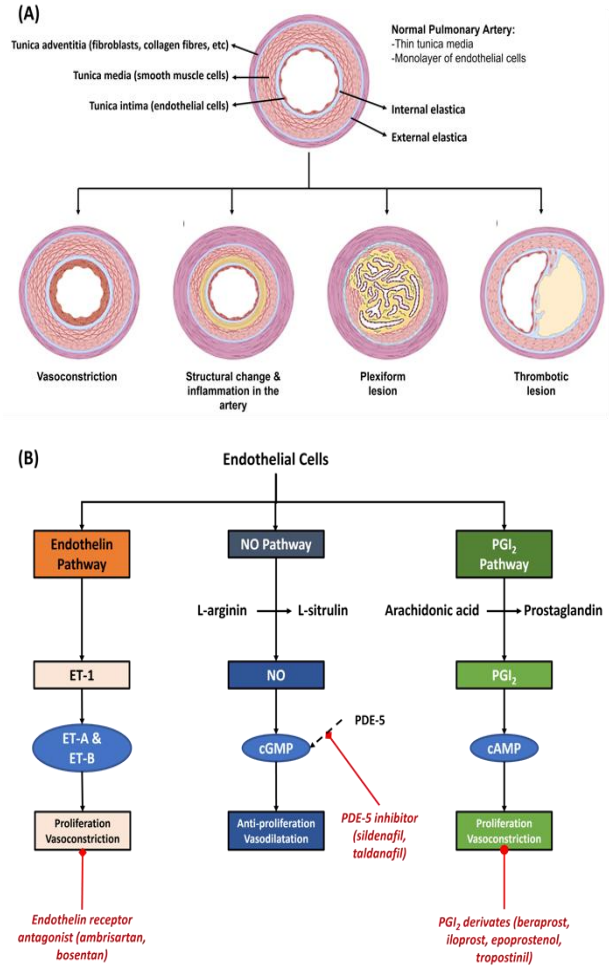
One of the most distinctive characteristics of pulmonary circulation and systemic circulation is their response to a low oxygen environment. In systemic circulation, decreased oxygen concentration triggers vasodilation, thus facilitating easier oxygen transport through increased blood flow. In contrast, pulmonary circulation boosts vascular tone to induce vasoconstriction, thereby raising PVR.[27,39] This mechanism aims to balance the distribution of oxygen throughout the lungs, prioritizing the most effective location, which is usually distant from hypoxic regions (Figure 4). Several conditions may induce hypoxic pulmonary vasoconstriction, such as high altitude, birth, and various lung disorders, including atelectasis, acute respiratory distress syndrome (ARDS), and obstructive pulmonary disease.[27,33,39]

In principle, during hypoxia (P_A <70 mmHg), blood flowing to alveoli will adjust the ventilation-perfusion ratio (V/Q). Small pulmonary arteries constrict to redirect blood to larger vessels and regions with better V/Q.[4,18] This phenomenon is considered physiological only until the hypoxia occurs in almost all parts of the lung, a condition known as global pulmonary hypoxia (GPH). Should GPH take place, the production of various vasoactive substances from lung parenchyma and endothelial cells may be disrupted. Therefore, most pulmonary arteries will undergo mass vasoconstriction, thus drastically increasing PVR.[38,39] In addition, vasoconstriction may also be triggered by elevated Ca^{2+} concentration within vascular smooth muscle due to the disruption of potassium-calcium channel.[40,41]

PULMONARY HYPERTENSION PATHOGENESIS & PATHOPHYSIOLOGY

In general, the underlying process of PH can be explained from both anatomical (endothelial dysfunction) and physiological (imbalance of vasoactive substances, vasoconstriction, and prolonged increased pulmonary vascular resistance) perspectives.[36,42,43] There are structural changes in all pulmonary blood vessels, from the pulmonary trunk to the capillary branch, especially at the histological level.[12,16,42] Hypertrophy of each tunica, fibroblast infiltration, plexiform lesion phenomenon, thrombotic lesion, and even lymphocyte perivascular infiltration can be found in pulmonary blood vessels (Figure 5A).[11,43,44] All of these pathological changes result in narrowing of the lumen, vasoconstriction, and finally an increase in PVR.

Current evidence shows endothelin receptor antagonists, phosphodiesterase 5 (PDE5) inhibitors, and PGI_2 derivatives are suitable for treating patients with PH. The main rationale for using these compounds is that the imbalance of vasoactive substances plays an important role in PH, as summarized in Figure 5 B. The production of vasoconstrictor and mitogenic compounds, such as endothelin (ET) and thromboxane A2 (TXA2), is increased in PH.[10,43] Endothelin is a potent vasoconstrictor and may serve as a parameter for predicting the severity of PH.[2] This substance binds to the ET receptor on the surface of smooth muscle cells, activating phospholipase C and increasing inositol trisphosphate levels.[16]



In addition, ET also activate the G protein-coupled receptor (GPCR) cascade, leading to an increase in intracellular calcium level.[16] Thromboxane A2, a product of arachidonic acid metabolism, has prothrombotic properties that can enhance platelet aggregation. Moreover, TXA2 also exhibits pro-mitogenic, pro-angiogenic, and pro-inflammatory effects.[43]

The decreased production of vasodilator substances such as NO and PGI_2 also plays a significant role in the vasoconstriction of pulmonary blood vessels. Endothelial cells synthesise NO with the help of Nitric Oxide Synthase (NOS). Cyclic Guanosine Monophosphate (cGMP) will be triggered

by NO to activate Protein Kinase G (PKG). This event decreases the intracellular level of Ca^{2+} and results in vasodilation. On the other hand, increased production of PDE5 by lung cells will hydrolyze cGMP to inhibit vasodilation.[5,10,43]

Similar to TXA2, PGI_2 is also a product of arachidonate acid metabolism mediated by PGI_2 synthetase. This substance will bind to the prostaglandin receptor to activate cAMP and cAMP-dependent protein kinase A (PKA), resulting in vasodilation as well as giving anti-proliferative and anti-thrombotic effects. In PH patients, the reduced production of NO and PGI_2 is caused by endothelial dysfunction.[10,11,16,43]

As previously mentioned, the main concept of PH pathophysiology is excessive vasoconstriction, which can cause a prolonged increase in pulmonary P_a and PVR.[2,42] Structural changes, inflammation, and lesions (thrombotic and plexiform) in pulmonary blood vessels lead to a chronic increase in PVR. The imbalance of vasoactive substances further contributes to elevated pulmonary P_a. Both circumstances increase the afterload of the heart, thus provoking the heart to adapt by increasing contractility and resulting in right ventricular hypertrophy.[13,16]

Cardiac output is maintained through right ventricular dilatation and increased heart rate. However, this adaptation forges additional stress on the cardiac walls and increases oxygen consumption. This phenomenon can be observed as leftward septal bowing in radiological imaging. Over time, stroke volume and cardiac output decrease, leading to right heart failure. If not properly treated, this condition may ultimately result in death.[13,16]

One of the etiologies of group 3 PH is COPD. Patients who have had COPD for a long time often suffer from chronic hypoxia, which can trigger chronic hypoxic pulmonary vasoconstriction. Additionally, pulmonary blood vessel dysfunction is commonly observed in COPD patients.[10,21,45] Pulmonary hypertension significantly increases the mortality of COPD patients, especially when there is a decline in forced expiration volume in one second (FEV_1), performance on the 6-minute walking test, or lung diffusion capacity.[17]

CONCLUSION

In PH patients, the atypical symptoms (exertional dyspnea, fatigue, chest discomfort or pain, dizziness, and palpitations) and high mortality rate, especially in high-risk populations (older age, chronic lung diseases, cardiac diseases, and autoimmune disorders), necessitate that clinicians be able to diagnose and treat patients early. A comprehensive understanding of the anatomy and physiological function of pulmonary circulation is essential for clinicians to diagnose and treat patients with pulmonary vascular diseases, particularly PH.

Pulmonary vascular resistance (PVR) is the resistance of pulmonary arteries to blood flow from the left atrium, reaching its peak during residual volume or total lung capacity, and its lowest point during functional residual capacity. Should pulmonary arterial pressure rise, recruitment and distention mechanisms are triggered to maintain PVR. Vascular smooth muscle tone actively regulates PVR, determined by various neural (sympathetic and parasympathetic) and humoral factors (vasoactive substances).

In principle, vascular endothelial dysfunction and imbalance of vasoactive substances are the main culprits of PH, causing excessive vasoconstriction, elevating PVR, and ultimately increasing pulmonary arterial pressure (P_a). Furthermore, alveolar hypoxia, which can be caused by chronic pulmonary diseases, aggravates vasoconstriction, thus further increasing PVR.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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