Continuing Cardiology Education

REVIEW ARTICLE

Classification and pathophysiology of pulmonary hypertension

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Keywords
Pulmonary hypertension, vascular biology, vascular remodeling

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Funding Information
No funding information provided.

***Continuing Cardiology Education*, 2018; 4(1), https://doi.org/10.1002/cce2.71**

Abstract

Pulmonary hypertension is a fatal disease of multiple etiologies that is estimated to affect over 100 million people worldwide. The disease is defined hemodynamically as a mean pulmonary artery pressure ≥ 25 mmHg at rest. Despite important advances in our understanding of the pathobiology of this disease and improvements in patient management, outcomes are still poor and no curative treatments are currently available. The complex nature of this disease requires detailed clinical evaluation for accurate diagnosis and treatment. Recent advances in clinical recognition, classification, and understanding of the underlying pathological processes in pulmonary hypertension have led to improved diagnostic testing and therapeutic options for patients. A hallmark of pulmonary hypertension is an increased pulmonary vascular resistance which leads to progressive elevations in pulmonary artery pressure, resulting in compensatory right ventricular hypertrophy and, ultimately, heart failure. Clinically, these pulmonary vascular changes initially present as nonspecific symptoms, including unexplained dyspnea on exertion, fatigue, chest pain, and syncope. Signs of right ventricular dysfunction are also frequently present. Common pathogenic features of pulmonary hypertension include sustained pulmonary vasoconstriction, vascular remodeling of the small pulmonary arteries, in situ thrombosis, and increased vascular wall stiffness, resulting in increased pulmonary arterial pressure due to increased pulmonary vascular resistance. Despite improvements in clinical classification and understanding of the underlying pathogenic mechanisms of pulmonary hypertension, current therapies are limited to supportive care and targeting pulmonary vasoconstriction. There remains a need to identify novel therapeutic targets in this disease. This review provides a succinct overview of the clinical classification and pathophysiology of PH that can be used as a reference by physicians and physician-scientists.

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Introduction

Pulmonary hypertension (PH) is a severe condition of multiple etiologies characterized by an elevation in mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, measured during right heart catheterization [1, 2]. Augmented right ventricular afterload and strain can result from sustained elevations in pulmonary blood pressure, ultimately progressing to right ventricular failure and death [3, 4]. PH is an increasingly recognized comorbidity to numerous common disease processes and is associated with poor prognosis, and therefore accurate diagnosis of this condition is imperative. Recent advancements in PH diagnosis have led to its recognition as a spectrum disorder which can be divided into five distinct groups based on etiology, common disease manifestations, clinical presentation and therapeutic strategies. Pulmonary arterial hypertension (PAH), the primary subtype of PH,

is characterized by progressive increases in pulmonary vascular resistance (PVR) primarily due to uncontrolled pulmonary vascular remodeling, sustained vasoconstriction and thrombosis in situ. These poorly understood disease processes, when left untreated, can significantly contribute to patient morbidity and mortality. The development of detailed clinical classification schemes, diagnostic criteria and novel therapeutics has lead to improved survival in PH over the past several decades, however, current therapies are unable to reverse disease progression and outcomes remain poor. In this review, we provide an overview of the current clinical classification and pathophysiology of PH.

Pulmonary Circulation

Understanding the physiology and pathophysiology of the pulmonary circulation is critical in the diagnosis and management of PH. The pulmonary circulation is responsible for carrying deoxygenated blood from the heart to the lungs and returning oxygenated blood back to the heart for delivery to the systemic circulation. Though the pulmonary circulation is faced with the entire cardiac output, low pressure and PVR is normally maintained due to abundance of small pulmonary arteries and capillaries with high cross-sectional area. More capillaries are recruited during exercise to maintain low PA pressure [5]. Elevations in PVR with subsequent increases in PA pressure are observed in the development of PH. According to the Poiseuille equation, PVR is directly proportional to the length of the blood vessel and viscosity of the blood and indirectly proportional to the radius of the blood vessel to the fourth power. Therefore, small reductions in the radius of blood vessels can lead to dramatic increases in PVR. Structurally, the pulmonary trunk branches into two pulmonary arteries and approximately 15 higher order branches to the pre-capillary level [6]. The pulmonary arteries are comprised of three layers: the inner intima comprised of pulmonary artery endothelial cells (PAECs), the middle medial layer comprised on pulmonary artery smooth muscle cells (PASMCs), and the outer adventitial layer comprised mostly of fibroblasts (Figure 1). Abnormalities in the function of all these cell types have been implicated in the development of PH.

Clinical Classification of Pulmonary Hypertension

PH is an increasingly recognized comorbidity to numerous common disease processes and is associated with poor prognosis, therefore accurate diagnosis of this condition is important. Advancements in the ability to clinically delineate subtypes of PH have led to improved therapeutic strategies and patient outcomes over the past several decades. Since pulmonary vascular disease can present across many medical disciplines, it is imperative that a broad range of general internists and specialists can accurately recognize the presentation of this condition.

The need to classify subtypes of PH was recognized in the 1970s, when reports of anorexigen-induced PAH initiated a meeting held by the World Health Organization (WHO) to define the underlying causes of PH. This meeting led to the first distinction between primary and secondary PH, and continued scientific discoveries into the pathogenesis of PH have prompted additional WHO meetings and improved recognition of the wide spectrum of this disorder. The most current PH classifications were defined at the 5th World Symposium on PAH in 2013 (Nice, France), with five separate groups identified based on shared disease histology and pathophysiology, clinical presentation, and therapeutic strategies (Table 1**,** Figure 2) [2]. The five groups of disorders that cause PH are: (1) PAH, (2) PH due to left heart disease, (3) PH due to chronic lung disease and/or hypoxia, (4) chronic thromboembolic PH (CTEPH), and (5) PH due to unclear or multifactorial mechanisms.

The advancements in PH classification have been aided by maintenance of worldwide clinical registries, initiated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) in the 1980s, which have aimed to identify factors affecting morbidity and mortality in patients with PAH. The development of detailed clinical classification schemes, diagnostic criteria, and novel therapeutics has lead to improved survival in PH over the past several decades, yet current therapies are unable to revert disease progression and outcomes remain poor.

The diagnosis of PAH can be challenging due in part to the nonspecificity of symptoms during early stages of pathogenesis. Physical exam and other noninvasive tests can help to delineate the subset of patients that require more invasive diagnostic procedures. It is important to note that changes in mPAP in PH may occur after significant alterations and damage within the pulmonary vasculature have occurred, so even small pressure elevations require extensive workup. Improvements in clinical diagnostic tools have led to the ability to distinguish subtler changes in structure and function of the heart and lungs in PH and to better estimate mPAP without cardiac catheterization.

Patients with PH typically present with symptoms indicating poor oxygen transport and impaired cardiac output, including unexplained dyspnea with exertion, fatigue, chest pain, syncope, hemoptysis, and Raynaud's phenomenon (associated with connective tissue disease)[7]. A high level of clinical suspicion is required for PH

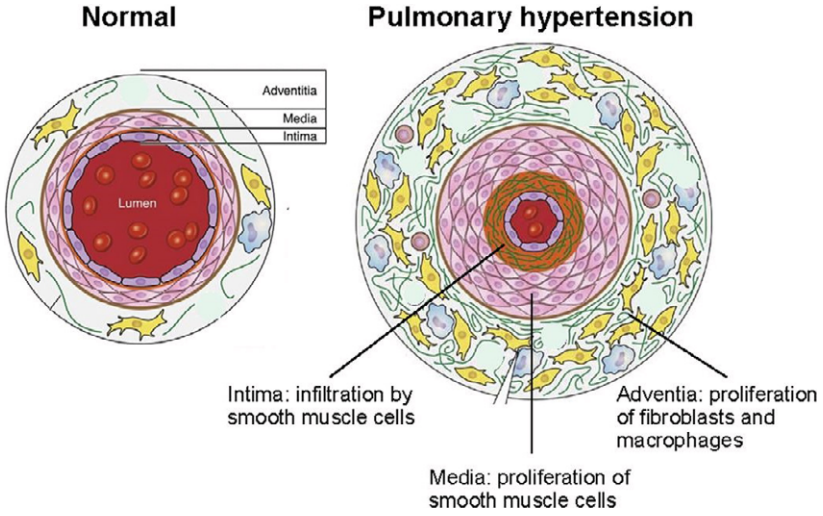

Figure 1. Vascular architecture in pulmonary hypertension. Cross-sectional representation of a normal pulmonary arteriole and a pulmonary arteriole in pulmonary hypertension. [Adapted from: Gordeuk et al.][39]

diagnosis due to the nonspecificity of these symptoms, and a detailed family history is important to identify potential hereditary PH cases. Clinical signs on physical exam may include jugular venous distension, hepatomegaly, presence of hepatojugular reflex, mottled extremities, cyanosis, diminished peripheral pulses, peripheral edema, and ascites. Cardiac auscultation can identify several abnormal sounds associated with PAH, including RV S3 and S4 sounds, accentuated pulmonic valve component (P2) of the second heart sound, systolic murmur indicating tricuspid regurgitation, diastolic murmur indicating pulmonary regurgitation, and a parasternal lift may be detectable.

Numerous invasive and noninvasive procedures are required for accurate diagnosis of PH, such as electrocardiography, pulmonary function testing, chest radiography, echocardiography, serologic testing, and right heart catheterization. Despite improvements in clinical diagnostics and understanding of the underlying pathogenic mechanisms of pulmonary hypertension, current mainstay therapies are limited to supportive care and targeting pulmonary vasoconstriction.

Group 1: Pulmonary Arterial Hypertension (PAH)

Group 1 PH, or PAH, is a category of diseases with the shared features of progressively increased PVR and mPAP due to obstructive changes within the pulmonary vasculature. The similarities between different types of PAH may reflect common underlying pathogenic mechanisms, which can ultimately lead to right ventricular failure and premature death. The causes of PAH include idiopathic, heritable, drug and toxin induced, and associated disorders such as connective tissue disorders, human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart diseases, and schistosomiasis. PAH can also result from pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis (Group 1′) and persistent pulmonary hypertension of the newborn (PPHN, Group 1″).

The median life expectancy in PAH was less than 3 years in the 1980′s before targeted therapies were available, with diagnosis occurring more often in young females [8, 9]. Outcomes currently remain poor even with the best available medications [10]. The epidemiology of PAH is constantly evolving, and the variability in disease etiology and limited number of studies available makes it challenging to accurately determine outcomes and survival [11]. In a recent prospective study of 482 patients diagnosed with PAH in the United Kingdom and Ireland, the estimated incidence of PAH was 1.1 cases per million per year with a prevalence of 6.6 cases per million in 2009 [12]. This study also found a change in the demographics of PAH, with younger patients having more severe and hemodynamic impairment but better survival compared to older patients with more comorbidities. Despite recent improvements in the classification and diagnosis of PAH, more studies are needed to better understand the epidemiology of this fatal disease.

Numerous gene mutations leading to a predisposition for the development of PAH have been discovered. Mutations in the bone morphogenetic protein receptor 2

Table 1. Current classification of pulmonary hypertension.

1	**Pulmonary arterial hypertension (PAH)**
1.1	Idiopathic PAH
1.2	Heritable PAH
1.2.1	BMPR2
1.2.2	ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3	Unknown
1.3	Drug and toxin induced
1.4	Associated with:
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart diseases
1.4.5	Schistosomiasis
1′	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″	Persistent pulmonary hypertension of the newborn (PPHN)
2	**Pulmonary hypertension due to left heart disease**
2.1	Left ventricular systolic dysfunction
2.2	Left ventricular diastolic dysfunction
2.3	Valvular disease
2.4	Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3	**Pulmonary hypertension due to lung diseases and/or hypoxia**
3.1	Chronic obstructive pulmonary disease
3.2	Interstitial lung disease
3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4	Sleep-disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental lung diseases
4	**Chronic thromboembolic pulmonary hypertension (CTEPH)**
5	**Pulmonary hypertension with unclear multifactorial mechanisms**
5.1	Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Adapted from Simonneau et al. [2] with permission from the American College of Cardiology Foundation.

(BMPR2) gene have been identified in approximately 75% of patients with a known family history of PAH and up to 25% of sporadic cases, with over 300 known independent mutations in this gene alone [13]. This gene product binds members of the transforming growth factor [TGF]-β superfamily of ligands. Rare mutations in other members of the TGF-β family, including activin-like receptor kinase 1 (ALK-1), endoglin (ENG), and mothers against decapentaplegic homolog 9 (SMAD9), have also been identified in PAH, highlighting the central importance of this signaling pathway in PAH. Several gene mutations without direct relation to the TGF-β family have also been found, including caveolin-1 (CAV1) and potassium two pore domain channel subfamily K member 3 (KCNK3), which has led to many important discoveries in the pathobiology of this disease [14, 15]. Despite advancements in genetic sequencing, over 20% of familial PAH cases have no identifiable mutation in disease-associated genes [13]. It is possible that PAH patients with no known genetic mutation may have an underlying genetic predisposition to PAH and are exposed to modifying factors during their lifetime that may lead to the development of PAH. These "second hits" could include genetic mutations, drugs, toxins, congenital heart defects, infections (e.g., HIV), or inflammatory states.

Many drugs and toxins are known to induce or be associated with development of PAH and are categorized by strength of evidence in the newest guidelines. However, the precise mechanisms of most of these compounds remain to be elucidated. Those with definite associated with PAH development include certain anorexigens (e.g., aminorex, fenfluramine, dexfenfluramine), toxic rapeseed oil, benfluorex, and selective serotonin reuptake inhibitors (SSRIs). The role of anorexigens in inducing PAH has long been established, with the use of anorexic agents in the preceding year or a total of more than 3 months having an odds ratio of 10.1 and 23.1, respectively [16]. The mechanism of anorexigens in PAH is largely unclear, though it is believed to involve serotonin biology given their interaction with the serotonin transporter to block serotonin uptake and the ability of serotonin to induce PASMC growth in PAH. Benfluorex, a hypoglycemic and hypolipidemic drug used in Europe to treat diabetes and metabolic syndrome, shares an active metabolite with fenfluramine and has recently been shown to trigger PAH development [17]. SSRI use during pregnancy increases the risk of PPHN and is also associated with mortality and clinical worsening in adults with established PAH [18].

Likely associated drugs with PAH include amphetamines, methamphetamines, L-tryptophan, dasatinib, while possibly associated drugs include cocaine, phenylpropanolamine, St. John's wort, chemotherapeutic agents, and interferon α and β. On the other hand, there has been no strong evidence for the association of PAH development with cigarette smoking, oral contraceptives, or estrogens. Interestingly, the use of a tyrosine kinase inhibitor, dasatinib, in the treatment of chronic myelogenous leukemia has been associated with severe PAH development, though improvement is seen with discontinuation of this drug [19]. Mechanistically, dasatinib paradoxically

Figure 2. Pulmonary hypertension is classified into five distinct groups based on the findings and recommendations from world experts at the most recent World Symposium on Pulmonary Hypertension (Nice, France, 2013).

decreases platelet derived growth factor (PDGF) that has been strongly implicated in PAH development as a mitogenic and promigratory stimuli for PASMCs.

An independent association of HIV with PAH development was first reported in the 1980-90s after improved HIV treatments led to increased recognition of noninfectious conditions, though the mechanisms in relation to PAH remain unclear [20]. Plexiform lesions are often seen in HIV-association PAH that are indistinguishable from idiopathic cases for PAH. Since HIV is not known to directly infect PAECs, the cell type most closely linked with plexiform lesion formation, more indirect mechanisms have been proposed such as the role of viral factors (e.g., Gp120, Nef, Tat), coinfection (e.g., hepatitis B, hepatitis C, human herpes virus 8 [HHV-8]), and host factor mediators. In addition, variables independently associated with PAH are often present in HIV patients, including intravenous drug use, which obfuscate the precise mechanistic connection.

PAH is also a severe vascular complication of connective tissue diseases, including scleroderma (systemic sclerosis), where it is associated with very poor prognosis and is the leading cause of death, as reviewed in detail

elsewhere [21]. The prevalence of PAH in scleroderma remains unknown since many patients are asymptomatic, but is estimated to be 10–15% [22]. Three-year survival rates in patients with PAH in scleroderma are less than 60%, therefore extensive screening for this disease is necessary [21].

Portopulmonary hypertension (POPH) is a form of PAH that is associated with portal hypertension with or without underlying chronic liver disease. PAH is estimated to affect 2–5% of patients with portal hypertension and up to 8.5% of those undergoing liver transplantation [23]. Although histologically similar to idiopathic PAH, POPH has a higher risk of death. A recent retrospective study of POPH patients demonstrated survival rates of only 85%, 60%, and 35% at 1, 3, and 5 years [24]. Treatment options typically combined vasodilator therapy and liver transplant, though outcomes remain poor and further randomized control trials are needed to improve management options.

Group 2: PH to Due Left Heart Disease

Group 2 comprises PH caused by left heart diseases, including left ventricular systolic dysfunction, left ventricular diastolic dysfunction, valvular disease, congenital/acquired left heart inflow/outflow tract obstruction, and congenital cardiomyopathies [25]. Most commonly this group of PH is found in patients with heart failure with preserved or reduced ejection fraction (HFpEF and HFrEF, respectively). Hemodynamically, this group is defined by a combination of mPAP ≥25 mm Hg, a pulmonary artery wedge pressure (PAWP) or left ventricular end-diastolic pressure (LVEDP) >15 mm Hg, and a normal or reduced cardiac output. The shared pathophysiology of this group involves a passive backward transmission of filling pressures that increases mPAP (e.g., loss of left atrial compliance, diastolic dysfunction, mitral regurgitation), a further increase in mPAP (e.g., endothelial dysfunction, vasoconstriction), and eventual worsening pulmonary vascular remodeling, right ventricular failure, and death.

Group 2 PH can be sub-classified into two categories based on the diastolic pressure difference (DPD, defined as [diastolic PAP – mean PAWP]) during right heart catheterization under resting conditions. These categories are isolated postcapillary PH (PAWP > 15 mmHg and DPD < 7 mmHg) and combined post and precapillary PH (PAWP > 15 mmHg and DPD ≥ 7 mmHg) [25]. This classification recognizes that a subset of patients have superimposed pulmonary vascular disease, and excludes previous terms such "reactive" or "out of proportion" PH.

Features and risk factors of Group 2 PH differ compared to PAH, as described in a recent cross-sectional study comparing the clinical, echocardiographic, and hemodynamic features of PH with HFpEF versus PAH [26]. Group 2 PH patients with HFpEF were older and had more cardiovascular comorbidities, worse exercise capacity and renal function, higher frequency of left atrial enlargement, lower frequency of right atrial enlargement, and less severe PH [26]. The risk factors that best differentiated PH with HFpEF from PAH were old age, the presence of hypertension and coronary artery disease, the absence of right atrial enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output [26]. These findings allow for the easier detection of PH with HFpEF, though it remains unknown why only some patients with HPpEF develop PH.

Though there is no validated treatment for Group 2 PH, the major goal has been to treat the underlying heart condition present. Previous clinical trials in Group 2 PH have resulted in little evidence of efficacy, likely due to the fact that the patient population is more heterogeneous than PAH, and can be divided into subgroups (isolated postcapillary PH and combined pre and postcapillary PH) (Figure 3). An early trial investigating epoprostenol, a prostacyclin analog, in Group 2 PH was terminated early due to a trend toward decreased survival. Endothelin receptor antagonists, used in PAH, have shown no benefit in heart failure patients. Promising results in Group 2 PH using the phosphodiesterase type 5 (PDE5) inhibitor, sildenafil, have recently emerged. A pilot study demonstrated that sildenafil use in Group 2 PH associated with left heart diastolic dysfunction improved mPAP, pulmonary capillary wedge pressure, RV function, pulmonary function, and quality of life [27]. A multinational, randomized, placebo-controlled clinical trial is now further investigating the efficacy of sildenafil in Group 2 PH [28].

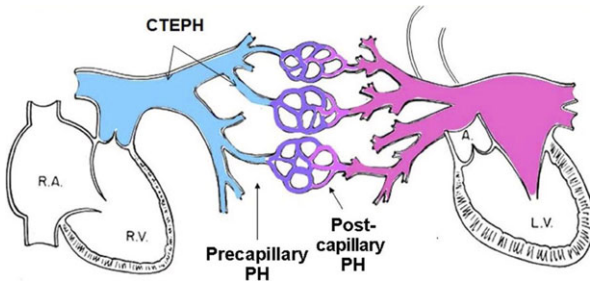

Figure 3. Schematic representations of pulmonary hypertension. Representation of site of initiation of elevated pulmonary arterial pressure of precapillary pulmonary hypertension, postcapillary pulmonary hypertension, and CTEPH. L.V., left ventricle; PH, pulmonary hypertension; R.A., right atrium; R.V., right ventricle. [Adapted from: Gordeuk et al.][39]

Group 3: PH Due to Lung Diseases and/or Hypoxia

The conditions associated with Group 3 PH include chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, sarcoidosis), other pulmonary diseases with a mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, chronic high altitude exposure, and developmental lung diseases [29]. Given the high prevalence of these associated lung diseases, it is often difficult to distinguish idiopathic PAH from Group 3 PH. However, Group 3 PH patients often have moderately to severely impaired ventilatory function, reduced breathing reserve, and characteristic airway and/or parenchymal abnormalities.

Group 3 PH patients generally have mild-moderate elevations in mPAP, correlating with the severity of the underlying disorder. Given the heterogeneity of this group, the true prevalence is difficult to determine and a high index of suspicion is needed clinically. PH in COPD is often viewed as common and relatively mild, though some patients develop more severe PH "out of proportion" to their underlying COPD and have nearly a 50% reduction in 5-year survival [30]. PH associated with ILD has a worse prognosis, with idiopathic pulmonary fibrosis patients having a fivefold increased 1-year mortality rate compared to PAH [31].

Two key pathophysiologic features underlying PH associated with hypoxia and COPD are hypoxic vasoconstriction and obliteration of the pulmonary vascular bed. Hypoxia induces endothelial cell damage, causing release of molecules such as endothelin that lead to neighboring smooth muscle cell vasospasm and proliferation. Eventual pathologic changes include arteriolar neo-muscularization, intimal thickening, medial hypertrophy, and adventitial collagen deposition. Although initial hypoxia-induced vasoconstriction is a reversible process, the pulmonary remodeling due to chronic hypoxia is largely irreversible.

Management for Group 3 PH typically includes treating the underlying disease process. Several drugs found to be efficacious in PAH have been tested in Group 3 PH with mixed results. Epoprostenol use in COPD-related acute respiratory failure showed a worsening in oxygenation, whereas iloprost improved gas exchange and exercise tolerance in a small, short-term study of Group 3 PH patients with associated COPD [32, 33]. Epoprostenol and bosentan both demonstrated symptomatic improvement in PH associated with ILD, but only short-term [34]. Larger and more long-term clinical trials are needed in Group 3 PH to assess the effects of PH-targeting drugs.

Group 4: Chronic Thromboembolic PH (CTEPH)

Group 4 comprises PH due to chronic thromboembolic disease that leads to prolonged occlusion of the pulmonary vasculature [35]. (Figure 3) These patients are often underdiagnosed and may have abnormal mechanisms of fibrinolysis or underlying hematological or autoimmune disorders contributing to a hypercoagulable state and poor resolution of thrombi. Underlying pulmonary arteriopathy or in situ thrombosis likely contributes to CTEPH development. This vascular remodeling may occur in the small muscular arteries and arterioles at the site of vessel occlusion, as well as in spared nonobstructed vessels secondary to the resulting high shear stress [35]. The precise mechanisms of why only a fraction of patients with acute pulmonary emboli develop CTEPH are poorly understood. A recent prospective, longitudinal study estimated the cumulative incidence of CTEPH in patients with acute pulmonary embolism without a history of other venous thromboembolism history to be 3.8% after 2 years [36].

In patients with known PH, VQ scanning is the preferred screening test for chronic thromboembolic disease, whereas pulmonary angiography is the gold standard for disease confirmation and to determine operability. Group 4 PH is unique in that surgical intervention with pulmonary thromboendarterectomy is potentially curable, though patients with distal vessel disease or significant comorbidities may not be surgical candidates [37]. Long-term anticoagulation is also indicated, and lung transplant and balloon pulmonary angioplasty have historically been used in select cases of CTEPH. Recently, the use of riociguat, a soluble guanylate cyclase stimulator, has been approved for the treatment of inoperable or persistent CTEPH after thromboendarterectomy [38]. Novel diagnostic and treatment modalities are needed for CTEPH to improve patient outcomes.

Group 5: PH with Unclear Multifactorial Mechanisms

Group 5 PH includes all other cases of PH that have unclear, multifactorial mechanisms. This encompasses hematologic disorders (sickle cell disease [SCD], beta-thalassemia, chronic hemolytic anemia, myeloproliferative disorders, splenectomy), systemic disorders (sarcoidosis, lymphangioleiomyomatosis, pulmonary histiocytosis), and metabolic disorders (glycogen storage disease, Gaucher disease, thyroid disorders). In addition, causes of tumoral obstruction, fibrosing mediastinitis, chronic renal failure, and segmental PH are included. SCD has been the most well characterized disease associated with Group 5 PH. Postcapillary PH in SCD is secondary to left ventricular dysfunction, whereas

precapillary PH may caused by vasculopathy from intravascular hemolysis, chronic pulmonary thromboembolism, or upregulated hypoxic responses. No randomized trials to date have found drugs to lower pulmonary pressure in SCD patients with precapillary PH [39]. Given the multiple etiologies of Group 5 PH, further research is needed to fully characterize this group of conditions and elucidate the pathophysiologic mechanisms of disease.

Pathogenesis and Pathophysiology of PH

While the mechanisms underlying the pathophysiology of Group 1 PAH have been studied to a great extent over the past several decades, leading to the discovery of many new potential drug targets, much less is currently known about Groups 2, 3, 4, and 5. Many of the mechanisms are clearly shared between all groups of PH, including vascular remodeling and elevated PVR. While some essential pathophysiological mechanisms specific to different PH groups were discussed above, the remainder of this section focuses on the development of PAH.

The fundamental mechanisms of elevations in PVR in PAH include sustained vasoconstriction, uncontrolled pulmonary vascular remodeling, and thrombosis in situ [40, 41]. PAH development is multifactorial and heterogeneous, and a wide variety of cell types within the PA vessel walls, including PAECs, PASMCs, fibroblasts,

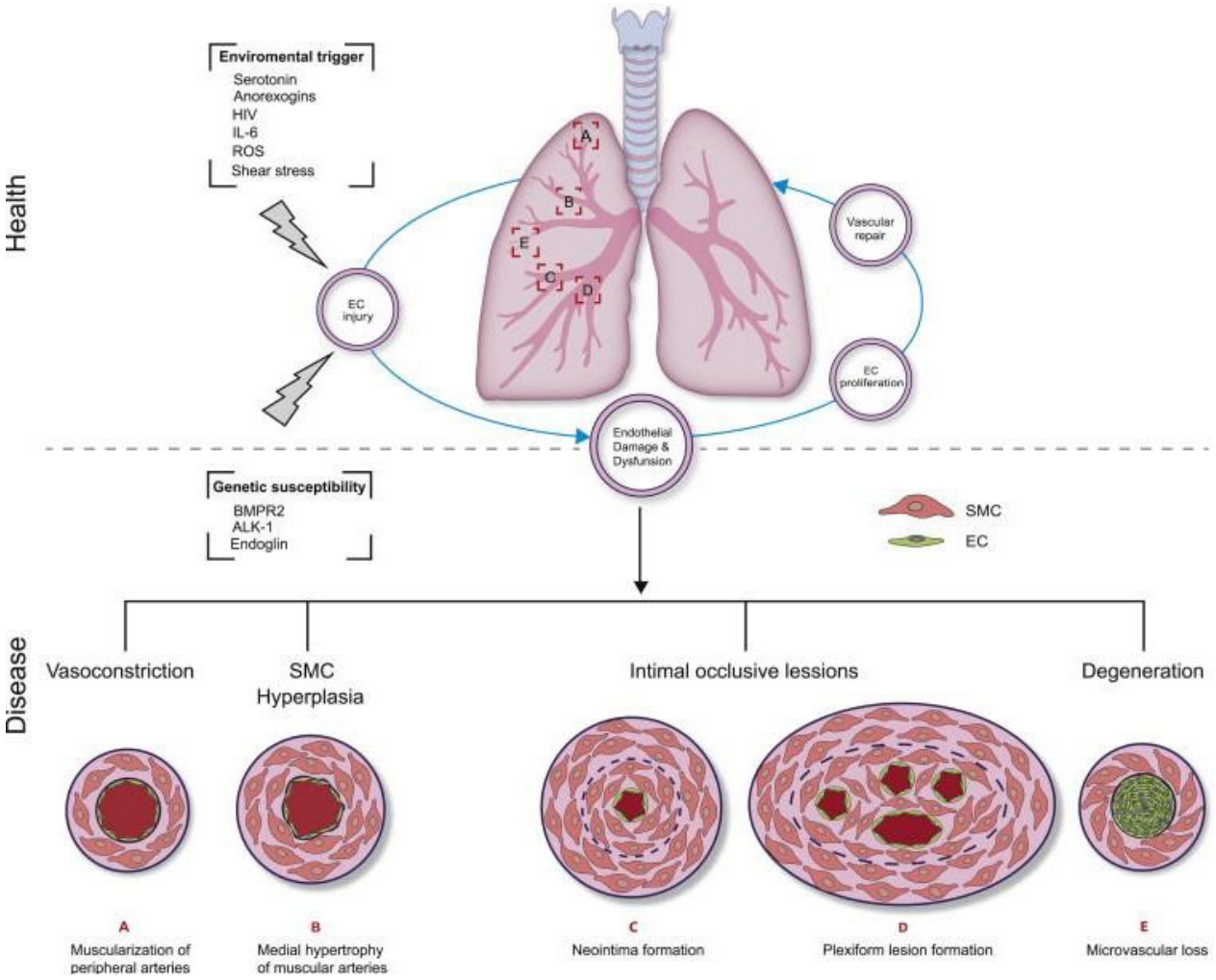

Figure 4. Pathophysiological mechanisms of PAH. Environmental insults can contribute to PAEC damage and injury. In the healthy state, physiological repair processes restore normal lung function via proliferation of nearby ECs and/or the recruitment of circulating endothelial progenitor cells (EPCs). In PAH, pulmonary vascular cell damage contributes to the degeneration of microvasculature and/or arteriolar remodeling. In patients with hereditary PAH underlying genetic mutations are associated with increased susceptibility to PAEC damage and injury. [Adapted from: Foster et al.][55] with permission from the Canadian Cardiovascular Society.

inflammatory cells, and platelets, are implicated in the disease process [42]. Initial vasoconstriction of the pulmonary vasculature leads to muscularization of peripheral arteries and medial hypertrophy of muscular arteries (Figure 1, 4). Genetic or toxic risk factors, discussed in the previous section, increase susceptibility to these changes. PAEC damage and dysfunction due to environmental triggers is also thought to be an early insult in PAH, and the repair process can lead to neointimal formation, vessel occlusion, and subsequent formation of plexiform lesions that increase PVR (Figure 4) [43, 44].

Pulmonary vasoconstriction is an early pathogenic process in PAH and can be induced by hypoxia, leading to narrowing of the luminal area of the PA branches. Hypoxia is known to inhibit voltage-gated potassium channels in PASMCs, which leads to opening of voltage-gated calcium channels due to membrane depolarization [45]. The resulting rises in cytosolic calcium levels can induce PASMC contraction and proliferation, a process specific to the pulmonary vasculature [46]. Down-regulation of potassium channels have been demonstrated in PASMCs and lungs of PAH patients [47, 48]. Several appetite suppressants implicated in the development of PAH, including fenfluramine, directly inhibit potassium channels and cause pulmonary vasoconstriction [49]. Importantly, sustained vessel constriction causes dysfunction of PAECs, leading to a chronic reduction in the production of vasodilators prostacyclin and nitric oxide (NO) and increased production of the vasoconstrictors endothelin 1 (ET-1) and thromboxane A2 [42]. These changes can also induce vascular remodeling, and therapies to target these pathways have been used [50]. Modulation of the NO pathway has been achieved using drugs that inhibit breakdown of cGMP (e.g., phosphodiesterase inhibitors) and stimulate guanylate cyclase (e.g., riociguat), or by directly inhaled NO replacement.

Pulmonary vascular remodeling is associated with marked medial hypertrophy due to unrestrained PASMC proliferation and apoptosis resistance and neointimal formation due to PAEC dysfunction and proliferation [44, 51]. These changes can lead to obstructive lesions which narrow the luminal space of vessels and impede blood flow, contributing to increased PVR [52]. Current investigations are underway to elucidate the mechanisms of abnormal cell proliferation contributing to the formation of pathogenic lesions. Other mechanisms of remodeling in PAH include increased adventitial matrix production and impaired proteolysis of extracellular matrix [42]. Evidence suggests that platelets may also play an important role in PAH pathogenesis given their ability to occlude vessels via thrombotic lesion formation and production of vasoconstrictive mediators, such as NO [53]. Platelets from idiopathic PAH patients have been shown to have reduced levels of endothelial nitric oxide synthase (eNOS) [54], which may contribute to vasoconstriction.

Conclusion

PH is a progressive and often fatal disease of multiple etiologies. Poor clinical outcomes persist despite improvement in our understanding of the pathogenesis and pathophysiology of these diseases. The complexity of PH requires detailed clinical evaluation for accurate diagnosis and management, though few treatments are available and are mostly limited to supportive care and targeting vasoconstriction rather than preventing or reversing uncontrolled vascular remodeling. There remains a need to identify novel therapeutic targets in this disease. The PH World Symposia have been essential in accurately classifying the different groups of PH based on the most recently available data. This article reviews the clinical classification and pathophysiology of PH and is intended to be used as a reference by physicians and physician-scientists.

Conflict of Interest

Both authors have nothing to disclose.

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