



A narrative review of research advances in hypoxic pulmonary hypertension

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Background and Objective: Hypoxic pulmonary hypertension (HPH) is a pathological syndrome characterized by pulmonary vasoconstriction and pulmonary vascular remodeling caused by hypoxia, which eventually leads to right heart failure or death. There are 2 stages of onset of HPH: hypoxic pulmonary vasoconstriction (HPV) and hypoxic pulmonary vascular remodeling (HPVR). It is an important pathophysiological link in the pathogenesis of chronic obstructive pulmonary disease (COPD) and chronic mountain sickness (CMS), and its severity is closely related to the course and prognosis of COPD and CMS. However, there is a lack of systematic review on the diagnosis, pathogenesis and treatment of HPH. The objective of this paper is to review the diagnosis, pathogenesis, treatment of HPH.

Methods: In this paper, the method of literature review is adopted to obtain the information about HPH. Based on the literature, comprehensive and systematic review is made. The diagnosis, pathogenesis, treatment of HPH are summarized.

Key Content and Findings: Right heart catheterization is the gold standard for diagnosing HPH. Hypoxia-inducible factor, oxidative stress, metal metabolism, ion channel, inflammatory cytokines, cell apoptosis and vascular factors are the main pathogenesis of HPH. The treatment of HPH includes long-term oxygen therapy, statins, prostaglandins, phosphodiesterase inhibitor and ET receptor antagonists.

Conclusions: Although great progress has been made in the pathophysiology and molecular biology of HPH, it is still unclear which factors play a leading role in the pathogenesis of HPH, and no breakthrough has been made in the treatment of HPH. It is believed that the specific mechanism will be revealed as the research continues, and earlier diagnosis and the development of more effective targeted drugs will be the focus of future research.

Keywords: Hypoxic pulmonary hypertension (HPH); hypoxic pulmonary vasoconstriction (HPV); hypoxic pulmonary vascular remodeling (HPVR); hypoxia-inducible factor (HIF)

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Introduction

Hypoxic pulmonary hypertension (HPH) is a kind of vascular disease caused by pulmonary hypoxia, characterized by pulmonary vascular remodeling and increased resistance, endothelial dysfunction, medium membrane smooth muscle cell proliferation, and extracellular matrix deposition (1). There are 2 stages of onset of HPH: hypoxic pulmonary vasoconstriction (HPV) and hypoxic pulmonary vascular remodeling (HPVR). It is an important pathophysiological link in the pathogenesis of chronic obstructive pulmonary disease (COPD) and chronic mountain sickness (CMS), and its severity is closely related to the course and prognosis of COPD and CMS (2,3). Due to the complexity of its pathogenesis and the late appearance of symptoms in the disease development, the patient's condition has usually progressed to the middle and late stage when clinical treatment is carried out, by which time, the condition cannot be greatly improved with treatment. Moreover, the currently available drugs cannot prevent or reverse the progression of the disease, so there is an urgent need to develop new diagnostic and therapeutic methods. Although the diagnosis and management of HPH have been reviewed in a literature, the included literature does not represent the latest research progress in this field due to its age, and the pathogenesis and clinical treatment effect of HPH have not been systematically reviewed. Therefore, this study aimed to review the

diagnosis, pathogenesis, and treatment of HPH, to provide a reference for the development of new diagnostic and therapeutic methods. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-259/rc>).

Methods

Information used to write this paper was collected from the sources listed in *Table 1*.

The diagnosis of HPH

According to the diagnostic criteria of the World Health Organization (WHO), the mean pulmonary artery pressure (mPAP) measured by right heart catheterization is used as the diagnostic gold index for HPH, and mPAP ≥ 25 mmHg at resting state at sea level is considered as the reference level (4). The Gold standard of WHO means it can be used as a diagnostic criterion for pulmonary hypertension, and other adjunct tests are used to screen high-risk populations or for patients who cannot undergo right heart catheterization. Supplementary tests can often provide clues to pulmonary hypertension when the patient cannot tolerate right heart catheterization, and non-invasive tests such as echocardiography can also provide a diagnosis. As the clinical manifestations of HPH are often masked by the primary disease and are atypical,

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	1/9/2020
Databases and other sources searched	PubMed, Index to Chiropractic Index to Chiropractic, MANTIS, ERIC (Educational Resources Information Center), AMED (Allied and Complementary Medicine Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), EMBASE/Excerpta Medica, Cochrane Database of Systematic Reviews
Search terms used (including MeSH and free text search terms and filters). Note: please use an independent supplement table to present detailed search strategy of one database as an example	Hypoxic pulmonary hypertension, hypoxic pulmonary vasoconstriction, hypoxic pulmonary vascular remodeling, hypoxia-inducible factor
Timeframe	Interesting topic: 1/6/2020; literature search: 1/9/2020; literature screening: 2021; paper writing: 2021; paper submissions: 2022
Inclusion and exclusion criteria (study type, language restrictions etc.)	None
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Jie Li and Tianci Chai conducted the selection independently, consensus was obtained by all researchers discussion
Any additional considerations, if applicable	None

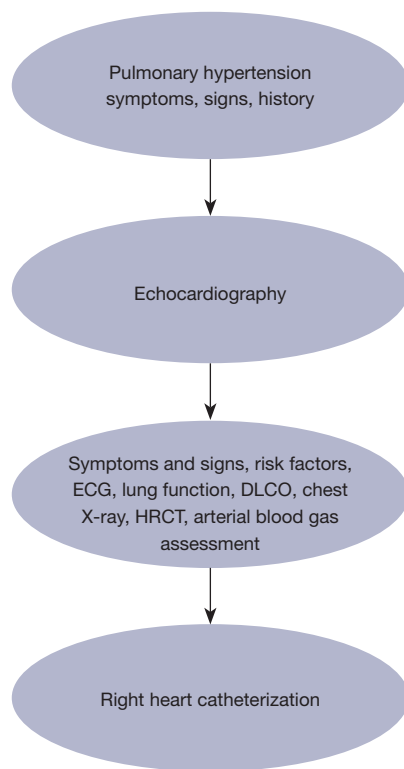


Figure 1 The diagnosis of HPH. ECG, electrocardiogram; DLCO, carbon monoxide dispersion; HRCT, high-resolution computed tomography; HPH, hypoxic pulmonary hypertension.

patients with high-risk factors should be alert to the possibility of pulmonary hypertension. As shown in *Figure 1*, we have organized the diagnostic methods of HPH.

Signs and symptoms

The symptoms of HPH include chest tightness, shortness of breath, chest pain, fatigue, syncope, and edema, and some patients experience dry cough and hemoptysis (5,6). The patient's physical signs can be related to right heart insufficiency and hypertrophy, including lifting pulse at the left sternal margin, P2 hyperactivity, third heart sound in the right ventricular auscultation area, total systolic murmurs in the tricuspid valve area and diastolic murmurs in the pulmonary valve area, jugular vein filling or even dilation, limb edema, hepatosplenomegaly, and so on (7-10).

Right heart catheterization

Right heart catheterization is the gold standard for the

diagnosis and evaluation of pulmonary hypertension. It can provide central venous pressure, right atrium pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, and blood oxygen saturation, and determine the degree of hemodynamic impairment (11,12). It can also be used to conduct an acute vasodilation test. Re-examination of right heart catheterization can be helpful in evaluating outcomes in patients who have already been treated.

Electrocardiogram

As a simple diagnostic method, although electrocardiogram (ECG) cannot exclude the existence of pulmonary hypertension, it can still provide a valuable diagnostic basis. Patients with pulmonary hypertension may have pulmonary type-P wave, right axis deviation, right ventricular hypertrophy, right bundle branch block, QTc prolongation, and so on (13-15).

Computed tomography (CT)

CT can not only measure the diameter of aorta, diameter ratio of pulmonary artery to ascending aorta, evaluate the vascular condition, right heart shape and size, atrial and ventricular wall thickness, but also contribute to the differential diagnosis of primary diseases, such as interstitial lesions, pulmonary space occupation, pulmonary artery space occupation, and so on (16,17).

Magnetic resonance imaging (MRI)

MRI can clearly image the right ventricle and pulmonary artery, and can also generate dynamic images to measure blood flow (18,19). It is an important non-invasive examination method to evaluate the shape and function of the right heart in patients with pulmonary hypertension (20,21).

Blood tests

Arterial blood gas should be monitored in patients with HPH, especially in those with primary COPD. The hemoglobin can be increased due to hypoxia compensation, and brain natriuretic peptide (BNP) and N-terminal type-B natriuretic peptide precursor (NT-proBNP) are often elevated to varying degrees, which are positively correlated with the severity of disease and the prognosis of patients (22-24). New diagnostic markers, such as asymmetric

dimethylarginine (ADMA), can evaluate the dysfunction of endothelial cells. The growth differentiation factor-15 (GDF-15), galectin-3, and macrophage migration inhibitory factor (MIF) are also under study (25-28).

The pathogenesis of HPH

Hypoxia-inducible factor (HIF)

HIF is an oxygen-sensitive transcription factor, which is the core of metabolic response to hypoxic stimulation. All of HIF-1, HIF-2, and HIF-3 are heterodimers composed of oxygen-sensitive α subunit (HIF-1 α , HIF-2 α , HIF-3 α) and oxygen-insensitive β subunit. In hypoxia, proteasome degradation of HIF-1/HIF-2 subunit is inhibited, resulting in nuclear translocation and binding to HIF-1 subunit (29). The heterodimer transcription factor binds to the hypoxic response element and results in the activation of more than 100 genes downstream to participate in the cellular adaptive response (30,31). In a low oxygen environment, HIF inhibits glucose oxidation and promotes glycolysis by increasing the content of pyruvate dehydrogenase kinase (32,33). As an acute response, this adaptive mechanism has short-term protection; however, chronic hypoxic stress and maladjustment of these protective mechanisms can induce HPH.

Oxidative stress

Reactive oxygen species (ROS) is considered to be an important signal molecule in oxidative metabolism, and its increase or decrease will eventually lead to pulmonary vasodilation or contraction (34). Complexes I, II, and III in the mitochondrial electron transport chain (ETC) are the main sites of ROS generation. Inhibition of pyruvate generation in aerobic respiration can reduce tricarboxylic acid (TCA) cycle and mitochondrial ROS generation in ETC. Therefore, ROS generation is reduced during hypoxia, leading to HIF activation and inhibition of the Kv1.5 channel. This process ultimately induces cell depolarization, and more calcium ions enter cytoplasm through L-type voltage-gated calcium channel, which leads to pulmonary vasoconstriction and promotes HPH progression (35-38).

Metal metabolism

Bioactive metals are an important part of enzymes, and as necessary cofactors of metabolic reaction, their metabolic

disorder has an important relationship with HPH. Some researchers have observed iron deficiency in HPH rats and believe that iron deficiency can be considered a mechanism to inhibit iron ion clusters, which is caused by substrate deprivation (39). Iron-sulfur clusters assembly proteins 1 and 2 (ISCu1/2) are responsible for assembling iron-sulfur clusters, and are necessary prosthetic groups of TCA cycle and mitochondrial complexes I, II, and III in ETC. It is also a direct inhibitory target of hypoxia-induced MIR-210 (40). In hypoxia, HIF induces erythropoietin expression and red blood cell production, thereby consuming iron through hemoglobin synthesis (41,42). Beyond a certain threshold, MIR-210 can reduce the expression of ISCu1/2, resulting in a decrease in the content of iron-sulfur clusters, ETC activity, and ROS production, leading to insufficient H₂O₂ reaching the plasma membrane (43,44). This process can shrink primary human pulmonary artery smooth muscle cells (PASMCs) and weaken Fe-S-dependent mitochondrial respiration (45). It promotes glycolysis in pulmonary arterial endothelial cell. In the acute phase, this mechanism facilitates the cellular stress response, while in the chronic state, it leads to mitochondrial metabolic disorder and reprogramming, promoting the emergence and development of HPH.

The pathogenesis of dysregulation of bioactive zinc ion metabolism in HPH has been established. It was found that Slc39a12 is a major regulator of hypoxia-induced pulmonary vascular remodeling. It encodes zinc transporter 12 (ZIP 12), promoting extracellular absorption and intracellular release of zinc in a variety of cells. It is an important regulator of zinc homeostasis. Study has shown that under hypoxia induction, ZIP 12 expression in pulmonary artery endothelial cells, smooth muscle cells, and stromal cells increases, resulting in increased expression of HIF1/2 and promoting the proliferation of these cells, indicating that imbalance of zinc homeostasis is related to the development of HPH (46).

Ion channel

The initiating link and the main pathological process of HPH is HPV. In the later stage of HPH, pulmonary vascular remodeling is the main pathophysiological change, and ion channels are involved in the contraction and proliferation of pulmonary vascular smooth muscle cells. According to biophysical and pharmacological characteristics, there are 3 kinds of potassium channels in pulmonary vascular smooth muscle: delayed rectifier

potassium channels (K_{DR}), calcium ion activated potassium channel (K_{Ca}), and adenosine triphosphate (ATP) sensitive potassium channel (K_{ATP}) (47). They play an important role in the vasomotor response of pulmonary vascular smooth muscle, such as determining resting membrane potential, regulating vascular tension, and influencing pulmonary artery smooth muscle proliferation. Intracellular potassium ion flows through 3 potassium channels, causing membrane depolarization, among which K_{DR} is the main potassium channel determining the resting membrane potential of PSMCs. Acute hypoxia inhibits K_{DR} function, leading to a decrease in K^+ outflow and membrane potential, inducing membrane depolarization, thus initiating calcium channel opening to allow extracellular calcium to enter the cell. Increased calcium level promotes the release of histamine, angiotensin II, and other neurotransmitters, resulting in HPV (48). The distribution of K_{Ca} is wide in PSMCs and it is directly involved in regulation of vascular tone. The opening of this channel can polarize the membrane potential and cause vascular dilation. When vascular smooth muscle cells depolarize and Ca^{2+} enters cells, K_{Ca} plays a negative feedback regulation role (49). Under normal circumstances, K_{ATP} is in the closed state. In acute severe hypoxia, a large amount of ATP is decomposed or synthesized in the cell, ATP concentration is significantly reduced, and this channel is opened, causing a significant decrease in vascular tension (50).

The increase of intracellular Ca^{2+} concentration is the key factor leading to the contraction of pulmonary vascular smooth muscle cells. When vascular endothelial cells are stimulated by hypoxia and inflammation, a variety of bioactive substances are released to activate voltage-gated calcium channels on the membrane of PSMCs, and Ca^{2+} influx increases, resulting in increased Ca^{2+} level in PSMCs, which leads to the occurrence of HPH (51,52).

Inflammatory cytokines

In recent years, a large number of studies have shown that lung inflammation plays an important role in the formation and development of HPH. In hypoxia, there may be a positive feedback effect of inflammation-inflammatory mediators-HIF-1-inflammatory mediators-inflammation. It has been shown that HIF-1 not only induces nuclear factor- κ B (NF- κ B) transcription by activating I κ B or phosphorylation of P65 residue Ser276 and enhancing nuclear shift of P65, but also amplifies NF- κ B signaling pathway by increasing toll-like receptors expression (53-55).

Furthermore, it promotes the production of a series of inflammatory mediators, the aggregation of inflammatory cells, and the damage effect on blood vessels. Hypoxia promotes inflammatory cell infiltration and inflammatory factor secretion in lung tissue, which is an important mechanism leading to pulmonary vascular remodeling. Inflammatory cells mainly infiltrate the outer membrane of blood vessels, mainly lymphocytes, especially CD8⁺T cells (56). Chronic vascular inflammation eventually leads to pulmonary vascular remodeling, and its severity is positively correlated with the thickness of the vessel wall. Endothelial cell injury is the key initiating link of vascular inflammatory pathological changes. Under the stimulation of hypoxia, vascular endothelial cells express some special proteins and markers, such as epidermal cell adhesion molecule-1, TGF receptor and E. Selectin, tissue factors, and so on, which initiates the endothelial injury process (57,58). After endothelial injury, the vascular endothelial barrier is damaged, and circulating inflammatory mediators and some growth factors can directly act on the vascular wall. Meanwhile, some external factors, such as vascular endothelial, can accelerate the changes of vascular structure and function when hypoxia occurs, ultimately leading to HPH. The synthesis and expression of cytokines [including monocyte chemokine-1, interleukin-1 (IL-1), IL-6, tumor necrosis factor- α (TNF- α), platelet-derived growth factor- α (PDGF- α), C-reactive protein (CRP), and macrophage inflammatory protein, among others] in circulation and lung tissue were shown to be significantly increased in HPH patients, suggesting that these cytokines and inflammatory mediators may be involved in the formation of HPH and correlated with its severity (59).

Cell apoptosis

Apoptosis is an important physiological process that causes PSMCs to decrease, thereby reducing pulmonary artery pressure. The proliferation of pulmonary smooth muscle cells and the decrease of apoptosis can increase the thickness of pulmonary arteriole wall, and lead to the constriction of pulmonary artery lumen, the increase of pulmonary vascular resistance, and the increase of pulmonary artery pressure (60,61). In physiological states, proteins that promote and inhibit apoptosis exist in cells to maintain the integrity of mitochondrial membranes by sensing cellular stress and response. The Bcl-2 family proteins control the permeability of mitochondrial membrane through conformational changes under stimulation, which is the key

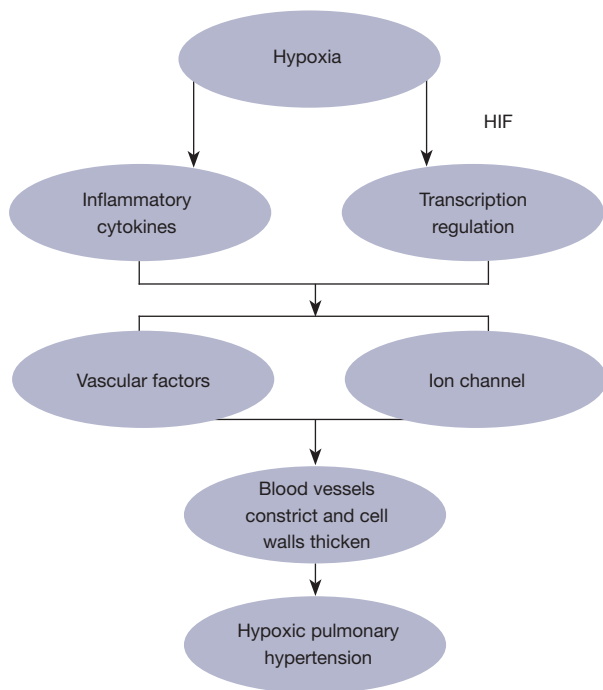


Figure 2 The pathogenesis of HPH. HIF, hypoxia-inducible factor; HPH, hypoxic pulmonary hypertension.

to mitochondrial apoptosis pathway (62). Under chronic hypoxia, the overexpression of Bcl-2 inhibits the expression of Bax, thus increasing the expression of anti-apoptotic and decreasing the expression of pro-apoptotic, leading to the proliferation and remodeling of pulmonary artery smooth muscle (63). In many animal experiments related to HPH, proliferation and apoptosis have been shown to co-exist in the pulmonary vascular cells of HPH rats. The expression of Bcl-2 was significantly increased in the hypoxia group, while the expression of Bax was significantly inhibited, ultimately leading to the proliferation and remodeling of PSMCs (64,65).

Vascular factors

Endothelial cells with barrier and endocrine functions located on the lumen surface of pulmonary vessels can secrete vascular active factors such as endothelin-1 (ET-1), nitric oxide (NO), thromboxan (TX) A₂, 5-hydroxytryptamine (HT), and prostacyclin (PGIs) under induction conditions. They also act on PSMCs by paracrine pathway including endothelin (ET) pathway, NO pathway, and prostacyclin pathway (66). Under hypoxic conditions, it is involved in the regulation of

vascular wall tension, smooth muscle cell proliferation and migration, inflammatory response, and thrombosis by blocking the synthesis of induced NO synthase, reducing the bioavailability of NO, up-regulating the expression of ET-1 receptor, reducing the production of PGI₂, and increasing the production of TXA₂ and 5-HT, which leads to increased pulmonary artery pressure (67,68). As shown in *Figure 2*, we have organized the pathogenesis of HPH.

The treatment of HPH

Long-term oxygen therapy

Besides being a common complication of COPD, HPH is a major factor in the increase of mortality. It is not clear whether long-term oxygen therapy can reduce pulmonary artery pressure in patients with COPD. Long-term low-flow oxygen intake can stabilize mean pulmonary arterial pressure and improves prognosis and survival (69). The ideal treatment for patients with high-altitude pulmonary hypertension (HAPH) is to relocate to low-altitude areas, and oxygen therapy is also an effective treatment for patients who cannot emigrate.

Statins

Statins are inhibitors of 3-hydroxy 3-methylglutaramidase A reductase, including lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin, among others. In addition to the effect of lowering blood lipids, recent studies have found that they still improve endothelial function, and exert effects of anti-inflammatory, antioxidant, and anti-proliferation, thus inducing cell apoptosis (70,71). Simvastatin can reduce pulmonary arterial pressure by inhibiting inflammatory cell invasion in COPD patients with pulmonary arterial hypertension (PAH) (72). Fluvastatin can inhibit the down-regulation of Caveolin-1 expression and prevent the formation of PAH in rats (73).

Prostaglandins (PGIS)

PGIS can expand pulmonary circulation and systemic circulation, inhibit platelet aggregation, inhibit smooth muscle cell migration and proliferation, delay pulmonary vascular remodeling, and inhibit ET synthesis and secretion (74-76). At present, the clinical application of PGIS includes intravenous eprostol, subcutaneous treprost, oral beprost, and inhaled eprost. The combination of these

drugs with phosphodiesterase type-5 (PDE-5) inhibitors has synergistic effects (77). There are few studies on PGIS analogs, and clinical trials with small samples have suggested that iloprost can improve V/Q ratio and exercise endurance (78).

Phosphodiesterase (PDE) inhibitor

PDE inactivates the second messenger cGMP of the prostacyclin pathway. Sildenafil is a highly selective PDE-5 inhibitor that prevents the degradation of cGMP and thus increases its diastolic action, as well as reducing pulmonary arterial pressure and improving hemodynamics (79). The therapeutic effect of sildenafil on arterial PAH has been confirmed, but its therapeutic value in HPH is being further studied. Vitulo *et al.* conducted a multi-center double-blind controlled experiment, in which sildenafil was shown to reduce PVR, improve body mass index, airflow obstruction, dyspnea, and exercise (BODE) index and quality of life in COPD patients, but did not significantly improve blood oxygen partial pressure (80). As for the efficacy of PDE-5 inhibitors, Zisman *et al.* conducted a clinical trial on the efficacy of sildenafil treatment (81). Compared with the control group, the sildenafil group showed no significant improvement in exercise tolerance, but exhibited improved arterial oxygen content, carbon monoxide dispersion (DLCO), shortness of breath, and quality of life. Despite this, there have been trials that have shown that sildenafil improves not only symptoms but also exercise endurance (82,83).

ET receptor antagonists (ERA)

ET was first discovered in 1988 and is considered the strongest vasoconstriction active substance to date. ET-1 was highly correlated with HPH. Valerio *et al.* treated 32 patients with pulmonary hypertension and COPD with bosentan or placebo. After 18 months, mPAP, PVR, and 6-minute walking test (6MWT) improved in the treatment group compared with the placebo group. However, most clinical trials showed that ERA had no significant effect on these patients (84). King *et al.* conducted a randomized controlled study on the efficacy of bosentan in the treatment of interstitial lung disease (ILD)-associated pulmonary hypertension. Compared with the control group, the quality of life, health, and dyspnea of patients in the bosentan group were not significantly improved (85). Trials have also shown that ambrisentan does not work in these patients, with the use of ambrisentan has even been associated with

accelerating disease progression and higher hospitalization rates (86).

Summary

The disease HPH is a complex pathophysiological process involving many kinds of cells and molecules, and its main inducement is hypoxia. Right heart catheterization is the gold standard for diagnosing HPH, and other methods, especially hematology and noninvasive imaging are also being developed. In the progression of HPH, there are many influencing factors and their interaction forms a complex network relationship. At present, the main treatments are aerobic therapy, statins, prostacyclins, ET antagonists, PDE inhibitors, and so on. With the development and application of new drugs and therapies, the survival rate and quality of life of patients with HPH have been greatly improved, but the long-term prognosis of HPH is still not optimistic, so earlier diagnosis and the development of more effective targeted drugs will be the focus of future research.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-259/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-259/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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