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REVIEW

High-altitude pulmonary hypertension: a comprehensive review of mechanisms and management

Xitong Yang[1,2,3] · Hong Liu[3] · Xinhua Wu[3,1,2]

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Abstract

High-altitude pulmonary hypertension (HAPH) is characterized by an increase in pulmonary artery pressure due to prolonged exposure to hypoxic environment at high altitudes. The development of HAPH involves various factors such as pressure changes, inflammation, oxidative stress, gene regulation, and signal transduction. The pathophysiological mechanisms of this condition operate at molecular, cellular, and genetic levels. Diagnosis of HAPH often relies on echocardiography, cardiac catheterization, and other methods to assess pulmonary artery pressure and its impact on cardiac function. Treatment options for HAPH encompass both nondrug and drug therapies. While advancements have been made in understanding the pathological mechanisms through research on animal models and clinical trials, there are still limitations to be addressed. Future research should focus on exploring molecular targets, personalized medicine, long-term management strategies, and interdisciplinary approaches. By leveraging advanced technologies like systems biology, omics technology, big data, and artificial intelligence, a comprehensive analysis of HAPH pathogenesis can lead to the identification of new treatment targets and strategies, ultimately enhancing patient quality of life and prognosis. Furthermore, research on health monitoring and preventive measures for populations living at high altitudes should be intensified to reduce the incidence and mortality of HAPH.

Keywords High-altitude pulmonary hypertension · Hypoxic environment · Pathogenesis · Diagnosis · Treatment strategies

Introduction

Pulmonary arterial hypertension (PAH) is a severe cardiovascular condition characterized by a resting mean pulmonary artery pressure (mPAP) of 20 mmHg or higher [1]; this leads to increased right ventricular load and can progress to right ventricular failure. The World Health Organization (WHO) reports a rising prevalence and mortality rate of PAH. The WHO classifies pulmonary arterial hypertension into five groups, see Box 1 [2].

High-altitude pulmonary hypertension (HAPH) is the third group of PAH, affecting individuals residing above 2500 m above sea level. This condition arises from prolonged exposure to a low-oxygen environment in high-altitude regions, leading to potential overactivity of the body's natural physiological responses; it is a prevalent condition among high-altitude residents. Diagnosis of HAPH requires meeting specific criteria, including mPAP > 30 mmHg and/or systolic pulmonary artery pressure (PAPs) > 50 mmHg. Other potential causes such as polycythemia, chronic obstructive, or interstitial lung disease, and neurological dysfunction must be ruled out before confirming a diagnosis of HAPH [3]. In a plateau environment, due to the enhanced vasoconstrictive response under hypoxic conditions, plateau residents are more likely to develop hypoxia-related adaptive changes, thereby affecting their mean pulmonary artery pressure levels. Therefore, the definition of HAPH may need to consider these unique physiological factors. Research on the Tibetan population has shown that at altitudes above 4500 m, the prevalence of chronic mountain sickness, such as pleocytosis, is increasing rapidly. Additionally, there has been a significant rise in the occurrence of plateau pulmonary hypertension, posing a serious threat to

✉ Xinhua Wu
13987286915@139.com

1 Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming, Yunnan, China

2 Medical School, Kunming University of Science and Technology, Kunming, Yunnan, China

3 The First Affiliated Hospital of Dali University, Dali, Yunnan, China

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Box 1 Pulmonary hypertension classification

Group 1: Pulmonary hypertension caused by pulmonary vascular disease;
Group 2: Pulmonary hypertension caused by left heart disease;
Group 3: Pulmonary hypertension caused by lung disease or hypoxia;
Group 4: Pulmonary hypertension due to chronic thromboembolic disease;
Group 5: A collection of various pulmonary hypertension syndromes caused by multiple diseases, including hemolytic anemia and sarcoidosis
Common features: pulmonary artery remodeling, increased pulmonary infiltrates, increased pulmonary vascular resistance, and right ventricular hypertrophy

the well-being, health, and safety of individuals living in high-altitude regions [4]. The research on HAPH holds significant scientific and clinical value due to its distinct pathogenesis and environmental influences. HAPH is a significant health concern worldwide, particularly in high-altitude areas such as the Kyrgyz Plateau, Ethiopia, the Andean region, and the Tibetan Plateau in China [5, 6]. A study on the Kyrgyz population showed that the incidence of HAPH may be as high as 14% among the long-term residents who have lived in high-altitude areas but cannot adapt to low oxygen [7]; the prevalence of HAPH in South America is 5–18% and is more common in men [8]. The prevalence of HAPH among people at an altitude of 3250 m in the Central Asian Plateau is approximately 6 to 35% [9]. Studies have shown that HAPH is rare among Tibetan people, but more common among Andes or plateau people who have migrated for less generations [7, 10]. This may be attributed to the Tibetan people on the Qinghai–Tibet Plateau having a longer history of settlement in the region, as well as possessing more significant physiological adaptations to the low-oxygen environment of the plateau, which reduces their susceptibility to chronic altitude sickness [11].

The symptoms of HAPH may not be noticeable until the advanced stages of the disease, leading to delayed diagnosis and treatment, which hampers the effectiveness of interventions and patient outcomes. Therefore, comprehensive research on HAPH is crucial not only for enhancing our comprehension of the condition, but also for advancing early detection and treatment strategies, ultimately improving the well-being and longevity of individuals residing in high-altitude areas. HAPH plays a significant health challenge not only locally, but also globally in high-altitude regions. Investigating this disease can contribute to shaping international health policies, particularly in light of global climate change and increased human migration to high altitudes, underscoring the importance of understanding and managing diseases in such unique environments. Furthermore, exploring HAPH aids in elucidating the broad impact of hypoxic conditions on human physiology, offering valuable insights for aerospace medicine, deep-sea diving medicine, and related disciplines.

There are several challenges in current research on HAPH. Firstly, limitations in transportation and medical resources in high-altitude regions make it challenging to gather extensive clinical data, hindering epidemiological studies. Secondly, the precise pathological mechanisms underlying HAPH remain incompletely understood, particularly regarding how hypoxia impacts pulmonary blood vessels through specific molecular and cellular pathways. Moreover, existing treatments often address symptoms rather than root causes, primarily derived from practices in sea-level regions and may not be fully suitable for HAPH patients in high-altitude areas. This review aims to comprehensively examine relevant HAPH research, delving into the biological foundations of pulmonary hypertension in hypoxic environments from pathophysiological mechanisms to clinical management. It also seeks to assess the efficacy and constraints of current treatment approaches. By consolidating existing research findings, the goal is to establish a more comprehensive theoretical framework to guide future investigations, particularly focusing on improved prevention and treatment strategies for PAH at high altitudes. Advancing these research avenues can not only enhance treatment efficacy for HAPH, but also deepen our understanding of this disease type, offering scientific insights for public health strategies in high-altitude regions globally.

Pathophysiological mechanisms of HAPH.

HAPH is primarily caused by prolonged exposure to a hypoxic environment, which has profound effects on the pulmonary vasculature. Hypoxia not only increases pulmonary artery pressure, but also causes a series of physiological and molecular changes, leading to pathological remodeling of pulmonary vessels. In the hypoxic environment, the initial pulmonary vasoconstriction is hypoxic pulmonary vasoconstriction in response to alveolar oxygen pressure. This response is an adaptive mechanism that optimizes systemic oxygen delivery by matching perfusion to ventilation to achieve maximum oxygen uptake [12, 13]. Persistent

alveolar hypoxia, as seen in patients with chronic hypoxia or chronic lung disease, can activate hypoxic pulmonary vasoconstriction (HPV), which may result in vascular remodeling, pulmonary hypertension (PH), and eventually heart failure [6, 14, 15], in Fig. 1. Under normal physiological conditions, the thickness of blood vessel walls is regulated by a delicate balance between cell proliferation and apoptosis [16, 17]. Disruption of this balance, with decreased apoptosis and increased proliferation, can lead to thickening of the vessel wall and eventual blockage of the vessel lumen, this process, known as vascular remodeling [18]. Vascular remodeling is a key factor in PAH due to abnormalities in pulmonary vascular structure and function. The three layers of the pulmonary blood vessel wall are adventitia, media, and intima [18], pulmonary vascular intimal damage, medial hypertrophy, and adventitial proliferation/fibrosis lead to progressive stenosis and occlusion of the pulmonary artery lumen, increasing pulmonary vascular resistance and causing pulmonary hypertension. As pulmonary artery pressure rises, the ventricle adjusts by enhancing contractility to maintain blood flow. However, if the right ventricular compensation threshold is surpassed, it can result in right ventricular hypertrophy, chamber dilation, fat deposition, fibrosis [3], and ultimately lead to death from right heart failure. Although the initial damage in HAPH is to the pulmonary vessels, right heart failure remains the leading cause of death in patients with HAPH [19, 20]. Right ventricular remodeling is characterized by initial adaptive hypertrophy, but may eventually decompensate, manifesting as dilatation, fibrosis, and functional failure [21, 22]. Right ventricular remodeling that occurs in HAPH includes right ventricular hypertrophy and right ventricular fibrosis. In the early stages of HAPH,

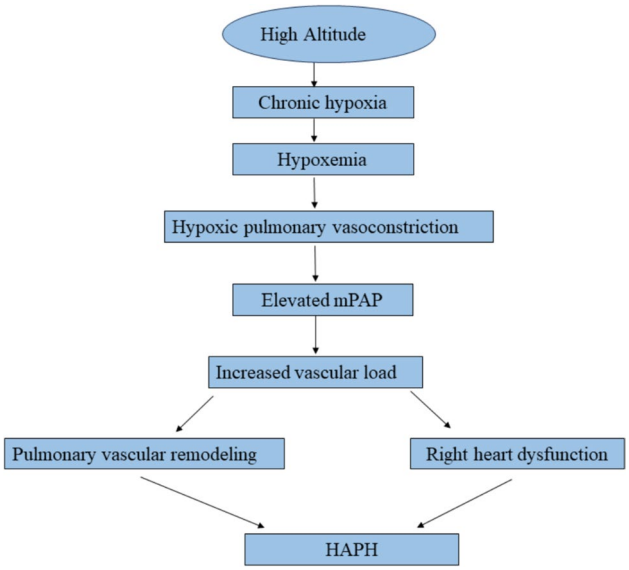

Fig. 1 Pathogenesis of high-altitude pulmonary hypertension

right ventricular remodeling is characterized by hypertrophic and hypercontractile remodeling, representing a compensatory response to increased afterload [23, 24]. However, as cardiac load increases, the adaptive response will gradually shift toward right ventricular hyperfunction, maladaptive remodeling, and right ventricular failure, accompanied by myocardial hypertrophy, apoptosis, and fibrosis [25]. Studies have confirmed that cardiac hyperfunction can lead to cardiac remodeling in failing hearts by increasing energy consumption [26].

The histological features of pulmonary hypertension are known to be intricate and diverse. A key pathological characteristic of this condition is the three-layer remodeling of distal pulmonary vessels, which involves excessive growth of endothelial cells, smooth muscle cells, and fibroblasts, along with the presence of inflammatory cell infiltration [27–29]. Hypoxia can result in focal disruption of the basement membrane of endothelial cells and thickening of the subendothelial space, which ultimately leads to heightened pulmonary vascular permeability. Additionally, overflow of cytoplasmic proteins from endothelial cells can trigger the activation of vascular wall proteases, subsequently initiating a cascade of proliferation reactions [30]. Hypoxia can induce endothelial cells to release more contractile mediators like endothelin-1 and platelet-activating factor to vascular smooth muscle cells, while decreasing the production of relaxing mediators such as nitric oxide (NO) and prostaglandins. Dysfunction in endothelial cells can result in heightened pulmonary vascular tone and vascular remodeling. In pathological scenarios, vascular smooth muscle cells and endothelial cells may exhibit increased heterogeneity, with their phenotypes changing based on the size and location of the pulmonary artery. Under pathological conditions, vascular smooth muscle cells and endothelial cells can show greater heterogeneity, and their phenotypes can change with the size and location of the pulmonary artery. At the same time, hypoxia can also cause vascular smooth muscle cells and vascular fibroblasts to excessive proliferation, this structural change can cause increased pulmonary vascular resistance and PAH [31].

In the hypoxic environment, the phenotype of smooth muscle cells changes from contractile to synthetic, which increases the cell's proliferation and migration capabilities. In addition, hypoxia also activates a variety of signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway, Rho/Rho-associated kinase (Rho/ROCK) pathway, phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, bone morphogenetic protein (BMP)/transforming growth factor-β (TGF-β) (BMP/TGF-β) pathway, nuclear factor kappa B (NF-kB) pathway, and Notch pathway. These pathways further promote the proliferation and migrate of smooth muscle cells [32, 33]. Endothelin, angiotensin II, prostacyclin, nitric oxide, carbon monoxide,

hydrogen sulfide, sulfur dioxide, estrogen, and other vasoactive molecules play an important role in pulmonary vascular remodeling through smooth muscle cells [34, 35]. Hypoxia-inducible factor-1α (HIF-1α), a transcription factor, is activated in hypoxic environments. This activation can lead to the induction of various genes related to erythropoiesis, energy metabolism, angiogenesis, and other biological processes [36, 37]. Specifically in the pulmonary vasculature, upregulation of HIF-1α directly increases the expression of angiopoietins, such as vascular endothelial growth factor (VEGF), and other molecules that support vascular remodeling. This process accelerates the proliferation and migration of vascular smooth muscle cells and endothelial cells [38, 39], the HIF signaling pathway under hypoxia/normoxia conditions is shown in Fig. 2. While progress has been made in understanding vascular remodeling through animal models and cell experiments, there is still a need for a deeper understanding of the mechanisms that regulate the proliferation, migration, hypertrophy, and apoptosis of pulmonary artery smooth muscle cells and endothelial cells.

Hypoxia also causes oxidative stress, which increases the production of reactive oxygen species (ROS), further leading to cell damage and inflammatory responses. Oxidative stress is a condition that occurs when ROS increases at the cellular level. There is more oxidative stress in a hypoxic environment, and hypoxia and the resulting pH are currently thought to be related to high levels of oxidative stress [43, 44]. ROS is a group of oxygen-derived species with one or more unpaired electrons in their outer orbital shell, making them highly reactive and unstable. Due to this instability, ROS can interact with and oxidize various cellular components such as lipids, DNA, proteins, and cell membranes, leading to alterations in their structure and function and triggering cell signaling pathways [45, 46]. ROS participates in a variety of physiological processes and is also related to pulmonary vascular reactivity as a second

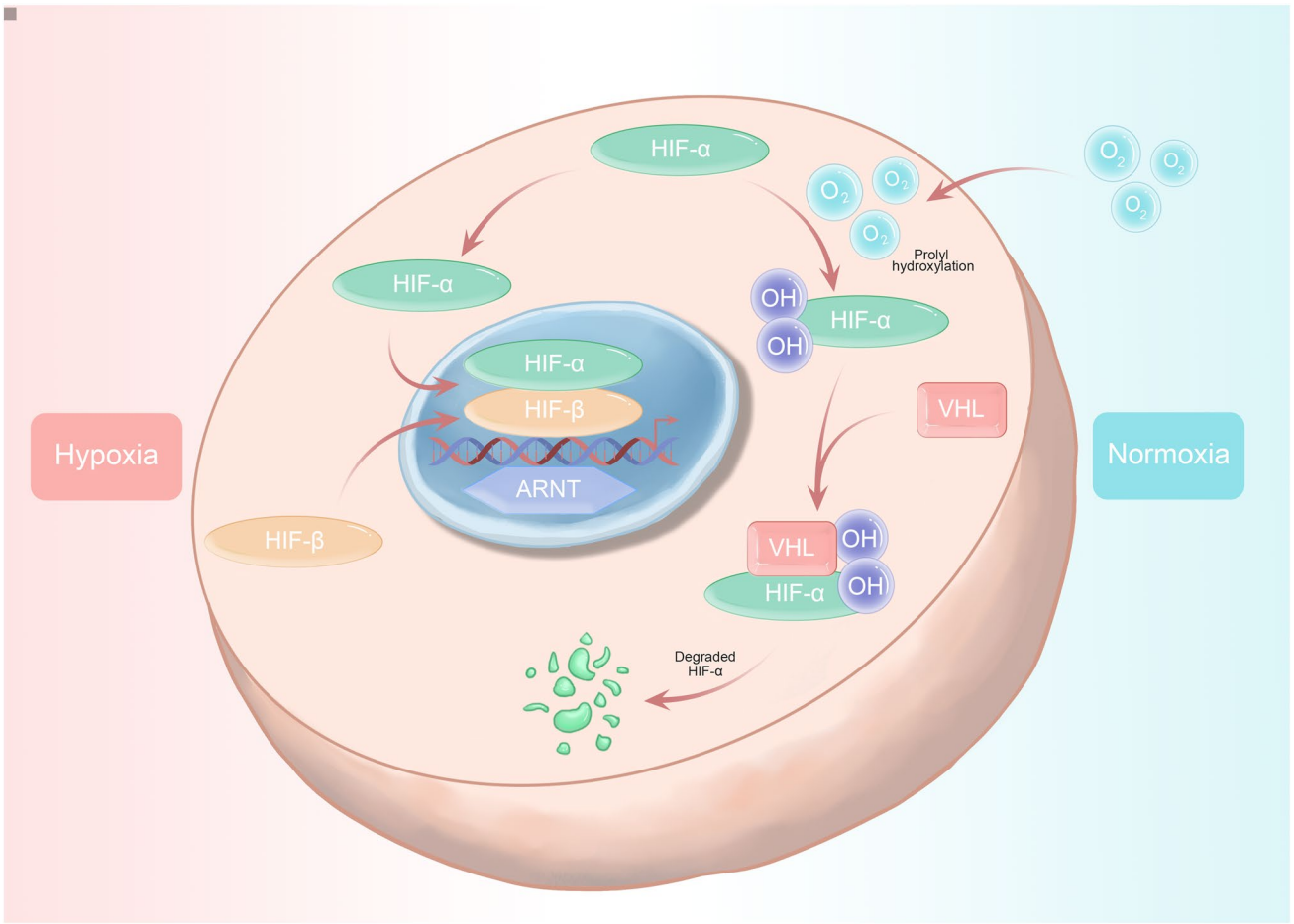

Fig. 2 HIF signaling pathway under hypoxic/normoxic conditions [40]. Under normoxia, the stability and activity of HIF-1α and HIF-2α are low as they are hydroxylated by oxygen-dependent proteolytic enzymes, recognized by the VHL protein complex, and degraded through ubiquitination [41]. In hypoxic conditions, inhibition of prolyl hydroxylase (PHD) activity leads to increased stability of HIF-1α and HIF-2α. The stabilized HIF-α subunit forms a complex with HIF-1β, translocates to the nucleus, and binds to the HIF response element, activating the transcription of downstream genes [42]

messenger [47]. However, when ROS is too much and cannot be absorbed by superoxide dismutase (SOD), catalase (CAT), glutathione peroxide Oxidative stress occurs when enzymes (GPX), peroxidoxin/thioredoxin (PRX/TRX), or metalloproteinases (MPs) are decomposed, and malondialdehyde is an oxidative stress biomarker[48], which is associated with total antioxidant capacity, CAT activity, and adverse clinical outcomes in patients with PAH [49]. It has been reported that patients with idiopathic pulmonary hypertension and rats with hypobaric hypoxia have higher plasma concentrations of malondialdehyde (MDA), a compound derived from oxidative stress-induced lipid oxidation [50, 51]. Similarly, increased levels of the DNA oxidation marker 8-hydroxydeoxyguanosine (8-OHdG) were found in endothelial cells [43, 52]. Furthermore, increased ROS may lead to inflammation, hypertrophy, cell proliferation, apoptosis, migration, and fibrosis [53], while also producing endothelial dysfunction [46].

Numerous studies have demonstrated that lung inflammation plays an important role in the formation and development of HAPH. In a hypoxic state, the human body may have a positive feedback effect of inflammation–inflammatory mediator–hypoxia inducible factor-1 (HIF-1) –inflammatory mediator–inflammation. HIF-1 stimulates the generation of various inflammatory mediators and the recruitment of inflammatory cells. Comprising an α subunit (HIF-1α) and a β subunit (HIF-1β), HIF-1β levels can be elevated under chronic hypoxia through the activation of NF-kB. Additionally, HIF-1 triggers NF-kB transcription by phosphorylating the p65 residue Ser276, facilitating the translocation of p65 into the nucleus. The protein degradation and transcriptional control of HIF-1α are intricately regulated by oxygen levels [54, 55]. Through in vivo and in vitro experiments in PAH rat models, it was found that HIF-1α can regulate mitochondrial dynamics in pulmonary vascular remodeling under hypoxic conditions by directly regulating the expression of dynamin-related protein 1 (Drp1), which in turn can cause hypoxia-induced mitochondrial dysfunction and hypoxia-stimulated PASMCs proliferation and apoptosis, that is, mitochondrial dynamics under hypoxic environment are involved in the remodeling of pulmonary vessels [56]. Studies have confirmed that the adhesion molecule CD146 and HIF-1α can trigger pulmonary vascular remodeling through the NF-kB pathway [57]. HIF and NF-kB are interdependent, NF-kB is a transcription factor that plays an important role in HIF-1α-related inflammatory responses and can be activated by hypoxia. The complete NF-kB pathway is responsible for cell inflammation in a hypoxic environment. It is required for gene expression and is also a key transcriptional activator of HIF-1α, with a high degree of dependence between HIF-1α and NF-kB signaling [58]. Inflammatory factors play a crucial role in the development of PAH. Hypoxia triggers the infiltration of inflammatory cells and the release of inflammatory factors in the lung tissue. Studies have demonstrated that exposure to hypobaric hypoxia for 24 h in humans leads to an upregulation of cytokines such as IL-1β, CXCL4, and CCRL2. Furthermore, the alterations in the expression of pro-inflammatory factors IL-1β and CXCR4 mRNA have been associated with the onset of acute respiratory syndrome symptoms [59]. At the same time, the inflammatory response may also lead to lung injury and fibrosis of pulmonary artery smooth muscle cells (PASMCs), leading to progressive damage to lung function [60]. Various inflammatory cells are crucial in the onset and progression of PAH. Macrophages, T cells, and B cells are known to gather in the lungs, particularly in perivascular regions, and are significant contributors to the development of pulmonary hypertension in both human patients and experimental models [29, 61]. In hypoxia-induced PH, lymphocyte antigen $6C^{low}$ nonclassical monocytes are recruited to the peripulmonary vasculature and differentiate into interstitial macrophages [62]. Many chemokines and cytokines, including tumor necrosis factor (TNF)-α, are upregulated in the serum of patients with PAH [63]. TNFα inhibits bone morphogenetic protein receptor 2 levels and signaling in human PASMC, and overexpression of TNFα in mouse lungs controlled by the human surfactant protein C gene induces pulmonary hypertension [64, 65].

Pulmonary vascular remodeling is influenced by both environmental factors (such as hypoxia, oxidative stress, and inflammation) and genetic factors [32, 66]. Individuals with HAPH may have shared genes that affect the response of pulmonary arterioles and/or veins to hypoxia, as well as the formation of smooth muscle cells from adventitial fibroblasts in weak and nonmuscularized pulmonary vessels. The discovery of bone morphogenetic protein receptor II (BMPR II) gene mutations in hereditary pulmonary hypertension is a milestone in the genetics of this disease [67, 68]. Bone morphogenetic protein receptor II, encoded by BMPR II, belongs to the TGF-β family and serves as a cell surface receptor. Mutations in its co-receptors, ALK1 (activin receptor-like kinase-1, ACVRL1) and ENG (endoglin), can lead to hereditary telangiectasia. Approximately 30% of individuals with these mutations develop pulmonary hypertension [69, 70]. Iranmehr discovered that the upregulation of myotubularin-related protein 4 (MTMR4), tropomodulin 3 (TMOD3), and vascular cell adhesion molecule 1 (VCAM1) genes could potentially impair the bone morphogenetic protein (BMP) pathway, hinder cell migration and tissue repair, impact leukocyte adhesion to endothelial cells, and modulate endothelial cell inflammatory reactions. These effects may contribute to a heightened vulnerability to HAPH in patients [5]. Hannemann's study revealed an association between the single-nucleotide polymorphism of the DDAH1 gene and plasma asymmetric dimethylarginine (ADMA) concentration, as well as a link between the

single-nucleotide polymorphism of the DDAH2 gene and the rise in ADMA levels during chronic intermittent hypoxia. ADMA, an endogenous inhibitor of NO synthesis, is upregulated in chronic intermittent hypoxia and exerts its effects on HAPH through the L-arginine-ADMA-NO pathway [71]. ADMA is a competitive inhibitor of endothelial nitric oxide synthase (eNOS), which plays a role in long-term exposure to chronic or chronic intermittent hypobaric hypoxia, the concentration of ADMA increases, competing with L-arginine to bind to the eNOS catalytic site, thereby competitively inhibiting eNOS activity, hindering the production of NO, and causing an increase in pulmonary artery pressure. Research on people susceptible to high-altitude pulmonary edema found that patients with elevated pulmonary artery pressure in high-altitude environments had increased free radical production and transpulmonary output in pulmonary blood vessels, increased pro-inflammatory cytokine production, and decreased NO bioavailability, suggesting that HAPH is related to free radical-mediated reduction in NO bioavailability [72].

The pathological phenotypic changes observed in individuals with HAPH (pulmonary artery smooth muscle cell proliferation, endothelial cell dysfunction, and inflammatory cell infiltration) may be attributed to a combination of pressure changes and other factors, including inflammation, oxidative stress, gene regulation, and related signal transduction factors [73]. The pathophysiological mechanisms of HAPH involve a wide range of molecular, cellular, and genetic levels. Through in-depth study of these mechanisms, future research has the potential to enhance our understanding of treatments for HAPH, identify new therapeutic targets, and establish a scientific foundation for clinical practice. With the progress in molecular biotechnology and gene editing technology, the investigation of these intricate mechanisms is expected to become more precise and efficient, offering improved prevention and treatment options for individuals residing in high-altitude areas.

Clinical manifestations and diagnosis

HAPH is a disease unique to plateau areas, and its morbidity and mortality rates are higher among people who have lived in the plateau for a long time and those who have migrated to the plateau for a long time. Clinical symptoms of HAPH patients typically include nonspecific signs such as fatigue, progressive dyspnea, and chest pain, along with additional symptoms such as headache, cognitive impairment, and further fatigue. The patient may exhibit early signs such as an increased second heart sound of the pulmonic valve, gradual enlargement of the right ventricle as the disease advances, and the presence of a systolic murmur of tricuspid regurgitation at the left sternal border. Additionally, individuals with HAPH may initially display an intensified second heart sound of the pulmonary valve. Progression of the disease can lead to further enlargement of the right ventricle and the audible systolic murmur of tricuspid regurgitation at the left sternal border. The study measured right atrial pressure, right ventricular systolic pressure and end-diastolic pressure, pulmonary artery pressure, and pulmonary circulation blood flow in patients with HAPH by inserting a catheter through the right internal jugular vein access, and calculated the right ventricular end-diastolic volume, pulmonary vascular resistance, and cardiac output. The amount and other functional indicators can reflect the preload, afterload, and contractility of the right ventricle. The results showed that patients with HAPH had varying degrees of reduced right ventricular function, indicating that the right ventricular function was impaired [74, 75]. In addition, plateau pulmonary hypertension and increased pulmonary blood flow resistance will also lead to increased right heart load and right ventricular myocardial hypertrophy, ultimately leading to irreversible damage to the myocardium and cardiac conduction system [74, 76]. Accurate assessment of right ventricular function in patients with HAPH can help early diagnosis, timely treatment and effective control of myocardial damage, and improve patient prognosis. In cases of right heart failure in HAPH patients, symptoms may include jugular venous distension, hepatojugular reflux, peripheral edema, hepatosplenomegaly, and ascites. Patients with late-stage HAPH may also experience symptoms such as dizziness, syncope, cough, hemoptysis, fatigue, and signs of right heart failure including jugular venous distention, hepatojugular reflux, hepatosplenomegaly, ascites, and pitting edema of the lower limbs [77]. In summary, the main symptoms of HAPH patients include dyspnea, exercise intolerance, and right heart failure. All factors jointly lead to premature death of HAPH patients [78]. The clinical diagnosis of HAPH presents challenges, with a high rate of missed and misdiagnosed cases. A thorough examination of the clinical manifestations of HAPH and enhancing diagnostic efficiency are crucial for improving the clinical management of this condition.

The current "gold standard" for diagnosing HAPH is the direct pressure measurement method using right heart catheterization. This involves inserting a cardiac catheter through a peripheral venous route to the pulmonary artery and right heart chamber to directly measure pulmonary artery pressure. However, this method is costly, highly invasive, and not suitable for routine clinical use [79]. As medical imaging technology advances, there is growing interest in using non-invasive imaging examinations as an alternative to invasive methods for diagnosing pulmonary arterial hypertension.

Echocardiography is the most commonly used method for screening HAPH. Studies on HAPH, both domestically and internationally, typically utilize echocardiography to assess

systolic pulmonary artery pressure (SPAP) and calculate pulmonary artery pressure using the modified Bernoulli equation. A diagnosis of HAPH is made when SPAP exceeds 50 mmHg. Doppler echocardiography calculates the tricuspid valve transvalvular pressure through the simplified Bernoulli equation ($\Delta P = 4\ V^2$, V is the maximum regurgitation velocity of the tricuspid valve), plus the right atrial pressure (usually the right atrial pressure is set at 10 mmHg), and the right ventricular pressure can be calculated. In the absence of right ventricular outflow tract obstruction or pulmonary artery stenosis, the right ventricular pressure is approximately equal to the pulmonary artery systolic pressure [80]. This detection method offers numerous advantages, including convenience, cost-effectiveness, and noninvasiveness. It can provide valuable information on various aspects such as increased pulmonary artery pressure, pulmonary artery widening, and enlargement of the right atrium and ventricle. Additionally, it can assess the impact of pulmonary artery pressure on the right heart system. With its broad screening capabilities and preliminary diagnostic value, echocardiography stands out among noninvasive examinations. However, it employs an indirect measurement method which may lead to underestimation or overestimation of pulmonary artery pressure levels. The accuracy of measurements is limited and can be influenced by subjective factors of the examiner. Therefore, it is essential to explore alternative noninvasive methods to enhance the accuracy of pulmonary hypertension diagnosis.

Cardiac magnetic resonance imaging (CMRI) is considered the gold standard for noninvasive assessment of right ventricular function. CMRI allows for precise measurements of right ventricle volume, mass, stroke volume, and ejection fraction with high accuracy and repeatability [81, 82], this imaging technique plays a crucial role in the early diagnosis and risk stratification of pulmonary hypertension. CMRI offers the benefits of being noninvasive, radiation-free, and highly reproducible, making it an optimal method for assessing the efficacy of pulmonary hypertension treatment [83].

Chest X-ray (CXR) examinations are an important screening tool for chest diseases, with good specificity in diagnosing pulmonary hypertension. However, its sensitivity is limited, and the presence of abnormalities in the image does not necessarily correlate with the severity of pulmonary hypertension. In cases of PAH, X-ray results may appear normal, especially in early stages. Only in advanced PAH cases, X-ray may show indirect signs such as enlargement of the right ventricle or pulmonary artery, and protrusion of pulmonary vessels, therefore, X-ray has obvious shortcomings in the diagnosis of PAH. Nevertheless, normal chest X-ray results can effectively rule out pulmonary hypertension due to moderate or severe lung disease and left heart disease. The basis for the diagnosis of pulmonary hypertension by X-ray chest radiography: (1) the diameter of the right lower pulmonary artery trunk is greater than 15 mm; (2) right ventricular enlargement signs: upturned apex, disappearance of the heart and waist; (3) protrusion of the pulmonary artery segment is greater than 3 mm; (4) the central pulmonary artery is significantly expanded, and the peripheral pulmonary field arteries suddenly become thinner; (5) the ratio of the diameter of the right lower pulmonary artery trunk to the transverse diameter of the accompanying bronchus is greater than 1.07, which is a comprehensive judgment of pulmonary hypertension [84]. However, the sensitivity is not high and it cannot directly diagnose HAPH. It can be used as indirect evidence to screen for HAPH.

CT detection is also an important method for the diagnosis of pulmonary hypertension. The maximum main pulmonary trunk diameter (MPAD) > 29 mm and MPAD/ascending aorta diameter (AAD) > 1 are currently recognized standards for multi-slice spiral CT diagnosis of pulmonary hypertension. At the same time, it can be understood the degree of interstitial lung disease, the size of the right ventricle and the position of the interventricular septum are evaluated. MPAD/AAD has a good correlation with mean pulmonary artery pressure, and this ratio can eliminate the influence of age and other factors on pulmonary artery and aorta diameter [82]. Computed tomography angiography (CTA), as a relatively objective and frequently performed clinical imaging examination, has higher data reliability than echocardiography, so it can be examined in patients with suspected PAH, and as a diagnostic algorithm for suspected PAH [85]. Studies have found through lung CTA examination that people with high mean pulmonary arterial pressure right heart catheterization ($mPAP_{RHC}$) are more likely to have right atrial enlargement, the ratio of right atrial diameter to left atrium diameter (rRLA), and the ratio of main pulmonary artery to aorta diameter (rPA) and left lower pulmonary artery-bronchus ratio (ABR) also increased with increasing $mPAP_{RHC}$. The left lower ABR and the left and right atrial diameter ratio are significantly correlated with HAPH and have a strong correlation with $mPAP_{RHC}$. Therefore, the left lower pulmonary artery-bronchus ratio and the left and right atrial diameter ratio also play an important role in the diagnosis of HAPH [86].

In addition, blood biomarkers such as brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) play a crucial role in diagnosing HAPH. These markers are notably increased in individuals with pulmonary hypertension and demonstrate a positive association with the severity of the disease [87]. Kosanovic [88] monitored the BNP levels of subjects at various altitudes, observing a significant increase in plasma BNP levels during prolonged stays at high altitudes. Conversely, levels dropped significantly upon return to low altitudes, suggesting that BNP levels may be lower at lower altitudes. These findings highlight the potential of BNP as an important biomarker

for the diagnosis and prognosis of HAPH in high-altitude hypobaric and hypoxic environment. Previous studies have shown that reduced oxygen partial pressure or hypoxia is an independent factor in regulating the synthesis and release of BNP [89]. Functional HIF-1α corresponding elements were found in the promoter sequence of the human BNP gene, proving that HIF-1α can induce the activation of the BNP promoter, the transcription of BNP mRNA, and the synthesis and secretion of BNP under hypoxic conditions [90].

Treatment and management

The current treatment methods for HAPH mainly consist of nondrug and drug therapies. Nondrug approaches involve intermittent oxygen therapy and descending to lower altitudes to enhance oxygen intake. Intermittent and short-term reoxygenation help prevent the remodeling of pulmonary artery function and structure, as well as the proliferation, migration, and phenotypic transformation of pulmonary artery smooth muscle cells in hypoxic conditions, thus effectively reducing hypoxia-induced pulmonary hypertension [91]. Oxygen therapy plays a crucial role in treating HAPH, particularly in individuals residing at high altitudes for extended durations. Research indicates that consistent use of low-flow oxygen inhalation can greatly enhance arterial oxygen saturation and decrease pulmonary artery pressure in patients [6, 92]. In addition, oxygen therapy can also reduce the burden on the heart caused by hypoxia and improve the patient's quality of life. In cases of acute mountain sickness, oxygen therapy has been shown to rapidly alleviate symptoms and potentially halt the progression of the condition [93, 94]. Yet, additional research is needed to fully understand the adherence and true efficacy of long-term oxygen therapy.

Drug treatments include endothelin receptor blockers, phosphodiesterase-5 inhibitors, prostaglandins, carbonic anhydrase inhibitors, and anti-inflammatory drugs, see Box 2 for drug classification. The pharmacological mechanisms are mostly related to reversing abnormal pulmonary vascular remodeling. However, vascular remodeling caused by hypoxia involves multiple mechanisms, drug treatment has limitations so drugs are not sufficient to reverse pulmonary vascular remodeling and prevent right ventricular dysfunction [95].

Box 2 HAPH therapeutic drug classification

Endothelin receptor antagonist	Tracleer, macitentan, ambrisentan
Phosphodiesterase-5 inhibitors	Sildenafil, tadalafil, vardenafil
Carbonic anhydrase inhibition	*acetazolamide*
Prostacyclin analogs	Epoprostenol, iloprost, treprostinil
Anti-inflammatory drugs	Quercetin, compound Danshen dropping pill (CDDP)
ROCK inhibitors	Fasudil

Endothelin, a powerful vasoconstrictor and smooth muscle stimulant, exerts its effects through two receptors: endothelin A receptor (ETRA) and endothelin B receptor (ETRB) [96]. ETRA is predominantly found in pulmonary artery smooth muscle cells, while ETRB is primarily located in vascular pulmonary artery epithelial cells with lower distribution in pulmonary artery smooth muscle cells [97]. Tracleer, the first oral antagonist of both ETRA and ETRB, has been approved for the treatment of PAH, and is also used in the treatment of HAPH. One study included plateau residents with HAPH, and the results showed that endothelin levels in HAPH were higher, and Tracleer treatment could reduce pulmonary artery systolic blood pressure more than oxygen inhalation [98]. Tracleer can restore the activity of pulmonary vascular endothelial cells (ECs) and NOS in rats exposed to hypoxia, promote NO synthesis, resist pulmonary vasoconstriction caused by hypoxia, expand pulmonary arteries, reduce pulmonary artery pressure, and reduce fluid penetration into the alveoli; NO, acts as a reducing agent, can effectively scavenge free radicals generated by oxidative stress, block lipid peroxidation of ECs, reduce inflammation, and slow down the development of HAPH [99].

In PAH, phosphodiesterases (PDEs) can convert cyclic guanosine monophosphate (cGMP) into 5′-GMP through hydrolysis and inactivate it, resulting in pulmonary artery vasoconstriction. [100]. Phosphodiesterase inhibitors enhance blood vessel dilation by blocking cGMP cleavage and increasing cGMP levels in vascular smooth muscle cells. Sildenafil, an oral PDE-5 inhibitor, was introduced in Europe in 2005. It inhibits the breakdown of cyclic guanosine monophosphate, leading to improved pulmonary artery systolic pressure and dilation of pulmonary artery blood vessels. Sildenafil lowers mean pulmonary artery pressure, enhances exercise tolerance, and does not impact systemic blood pressure [101].

Prostacyclin, prostaglandin I2, is a systemic and pulmonary vasodilator that induces pulmonary vascular smooth muscle relaxation by promoting intracellular cAMP production and inhibits smooth muscle growth and platelet aggregation [102, 103]. Studies have found that the activity of PGI2 synthase and its metabolites in pulmonary arteries isolated from PAH patients were reduced [104]. Therefore, prostacyclin analogs can be used in patients with PAH. Epoetin was the first prostacyclin analog approved by the FDA in 1995 for the treatment of PAH. Other prostacyclin analogs include iloprost, treprostinil, and so on.

Acetazolamide is a carbonic anhydrase inhibitor and weak diuretic that reduces bicarbonate reabsorption in the proximal tubule of the kidney, promotes diuresis, increases cerebral blood flow, and stimulates ventilation through metabolic

acidosis [105]. Research indicates that acetazolamide has the potential to alleviate pulmonary hypoventilation and enhance pulmonary circulation in individuals with chronic mountain sickness. This can lead to a decrease in secondary polycythemia and pulmonary vascular resistance. Due to its favorable side effect profile, acetazolamide is considered safe and efficient for prolonged use in managing chronic mountain sickness, showing comparable efficacy to long-term treatments for patients with HAPH [106].

Anti-inflammatory drugs have the ability to target multiple aspects of the inflammatory response, thereby inhibiting HAPH and vascular remodeling resulting from inflammation. Quercetin has been shown to inhibit signaling pathways associated with the inflammatory process, such as the phosphorylation of mitogen-activated protein kinases (MAPKs), nuclear factor κ-Bkinase (Iκ B kinase, IKK) α/β inhibitor, activation of cAMP response element-binding protein (CREB), activation of transcription factor 2 (ATF2), and nuclear factor κ-B p65, blocks NF-κB p65 from entering the nucleus. The translocation improves the inflammatory response by blocking the activation of MAPK and NF-κB signaling pathways [77]. Quercetin increases antioxidant response by increasing nuclear factor-erythroid 2-related factor 2 activity and reducing pro-inflammatory cytokine levels [107]. Inflammation plays an important role in the occurrence and development of HAPH, so quercetin can be used in the treatment of HAPH.

ROCK, an essential intracellular signaling molecule, plays a crucial role in regulating vasoconstriction and cell proliferation. There are two distinct subtypes of ROCK, ROCK1, predominantly found in the lungs and liver, and ROCK2, primarily located in the heart and brain. Fasudil, a Rho kinase inhibitor and vasodilator, has been approved for treating cerebral vasospasm. In animal models of hypoxic pulmonary hypertension, fasudil has demonstrated the ability to reduce PAP and pulmonary vascular resistance. Clinical studies have further supported its short-term efficacy and safety in treating patients with HAPH [108].

The angiotensin II receptor antagonist irbesartan demonstrated a reduction in pulmonary hypertension and left ventricular systolic dysfunction in a rat model of HAPH. The therapeutic impact of irbesartan could be attributed to the decrease in inflammatory factors like interleukin 1 and C-reactive protein, inhibition of vasoconstrictor factors and inflammatory mediator's release, or alteration in specific intestinal flora composition [109]. However, the precise mechanism of action remains elusive.

Limitations and prospects

Despite recent advancements in the study of high-altitude pulmonary hypertension, significant limitations persist in understanding its pathophysiological mechanisms through basic experiments and clinical trials. The precise pathological mechanism of HAPH remains elusive, with current research primarily focusing on pulmonary vasoconstriction and structural remodeling resulting from hypoxia. However, there is a lack of comprehensive investigation into the molecular mechanisms underlying how hypoxia triggers these changes. While the role of HIF in the hypoxia response is well-established [110, 111], further exploration is needed to elucidate the specific regulatory network of HIF in HAPH and its interactions with other molecules and signaling pathways.

Currently, most HAPH studies are based on animal models, especially rodents [112, 113]. However, physiological and pathological differences between animal models and humans may limit the translatability of research results. The structure and function of the pulmonary arteries in rodents are significantly different from those in humans, which may affect the assessment of a drug's effectiveness. In addition, animal models are often conducted under acute or short-term hypoxic exposure conditions, whereas plateau residents experience long-term chronic hypoxia, a difference that may affect the extrapolation of study results.

In clinical research, clinical trials of HAPH face many challenges, including difficulties in patient recruitment, complex trial design, and long follow-up times. Due to the particularity of the plateau environment, there are practical difficulties in conducting large-scale, long-term clinical trials. In addition, most current clinical studies have small sample sizes, making it difficult to obtain statistically significant results. Therefore, existing clinical data provide limited guidance on treatment options for HAPH.

Future research on HAPH should emphasize exploration at the molecular level, focusing on key molecules involved in the hypoxic response and their signaling pathways. While HIF has been extensively studied, other hypoxia-related molecules like NADPH oxidase, endothelin-1, and VEGF should also be investigated. Additionally, investigating the role of novel molecular targets such as noncoding RNA, including microRNA and long noncoding RNA, could offer new insights for treatment HAPH [114]. Gene therapy, as a cutting-edge technology, holds significant promise for the treatment of HAPH. Gene editing technologies, like CRISPR/Cas9, offer precise methods for modifying genes associated with HAPH to achieve therapeutic outcomes. By targeting the HIF-1α gene and regulating its stability and activity in hypoxic conditions, gene editing can effectively alleviate the pathological manifestations of HAPH [115]. Additionally, gene editing can be utilized to correct gene mutations linked to HAPH and address the root cause of the disease. Studies have found that more than 80% of HAPH patients have bone morphogenetic protein receptor II (BMPR2) mutations. By editing the BMPR2 gene with CRISPR-Cas9 technology, BMPR2 knockout resulted in reduced fibroblast proliferation

and BMPR2 mRNA expression, providing new clues to the impact of BMPR2 on the blood vessel wall in diseases such as high-altitude pulmonary hypertension [116]. Treatment of endothelial Nos3-knockout mice using endothelial cell-targeted nanoparticles to deliver CRISPR-Cas9/guide RNA plasmid DNA inhibited occlusive pulmonary vascular remodeling and attenuated severe pulmonary hypertension in Egln1Tie2Cre mice. Genetic restoration of Cav1 expression in Egln1Tie2Cre mice normalizes nitrative stress, reduces pulmonary hypertension, and improves right heart function [117]. In gene therapy for HAPH, both viral and nonviral vectors can be employed to introduce genes that encode specific proteins into pulmonary vascular cells. The introduction of genes encoding angiogenesis inhibitory factors into pulmonary vascular endothelial cells can suppress abnormal angiogenesis and mitigate the pathological changes associated with HAPH [118]. RNA interference technology can target specific mRNA molecules to inhibit their translation and expression. This technology can be utilized to silence HAPH -related genes, such as HIF-1α and ET-1, to reduce their overexpression in hypoxic conditions, thus alleviating the pathological changes of HAPH. RNA interference technology is characterized by its high specificity and effectiveness, positioning it as a potentially significant tool in gene therapy for HAPH [118].

HAPH is a multifaceted disease influenced by various factors, presenting challenges in both research and treatment. While recent studies have advanced our understanding of its pathological mechanisms, animal models, and clinical trials, there are still significant limitations. Future investigations should focus on exploring molecular targets, personalized medicine, long-term management approaches, and the integration of interdisciplinary methods. Leveraging cutting-edge technologies like systems biology, omics technology, big data, and artificial intelligence can help us gain a comprehensive understanding of HAPH pathogenesis, identify new treatment targets, and enhance patient quality of life and prognosis.

Personalized medicine is an important direction for future medical development. For patients with HAPH, developing personalized treatment plans based on multiple factors such as genes, phenotypes, and living environment will help improve treatment effects. Genetic testing can be used to determine a patient's response to a specific drug, thereby optimizing drug selection and dosage [118, 119].

Prevention strategies are crucial for residents and workers in high-altitude plateau areas. These strategies may include training to enhance adaptability to the plateau environment, maintaining a balanced lifestyle, implementing appropriate work schedules, and regular health monitoring. Incorporating nutritional supplements and aerobic exercise training can boost the body's ability to withstand low-oxygen levels and decrease the likelihood of developing HAPH [120, 121]. In cases where HAPH is already diagnosed, long-term medication management plays a pivotal role. It is essential to investigate new medications and combination therapies to alleviate symptoms and improve the overall prognosis.

Systems biology is an integrative research approach that aims to uncover the underlying complexity of biological processes by analyzing biological networks and pathways systematically. In the context of research on HAPH, systems biology can be utilized to map out hypoxic response networks, pinpoint key regulatory elements, and identify potential therapeutic targets. High-throughput technologies like proteomics, transcriptomics, and metabolomics play a crucial role in conducting comprehensive molecular analyses of both HAPH patients and animal models to develop systemic models. By integrating various omics data levels including genomics, epigenomics, transcriptomics, proteomics, and metabolomics, researchers can gain a profound understanding of the pathological mechanisms involved in HAPH. Genomic studies can shed light on genetic variations linked to HAPH; epigenomic studies can uncover hypoxia-induced epigenetic alterations, while transcriptomic and proteomic analyses can elucidate dynamic changes in gene expression and protein levels [122–124].

The utilization of big data and artificial intelligence technologies is on the rise in biomedical research. By analyzing large datasets, researchers can extract valuable insights to aid in the diagnosis, treatment, and prevention of HAPH. Machine learning algorithms are employed to create prognostic models for HAPH patients, supporting clinical decision-making [125]. Furthermore, artificial intelligence plays a role in drug development by expediting the discovery of new drugs through virtual screening and computational simulations.

The research on HAPH is at the forefront of multidisciplinary studies. Breakthrough progress can only be achieved through extensive cooperation and continuous innovation. Future research in this area necessitates the attention and support of society as a whole. With collaborative efforts, effective treatments are expected to be discovered in the near future, providing positive outcomes for the majority of residents and workers in plateau regions.

Conclusion

HAPH is a severe and complex pathological condition primarily triggered by prolonged exposure to hypoxic environments at high altitudes. The pathogenesis of HAPH involves various factors, such as vascular remodeling, endothelial dysfunction, inflammatory response, and genetic predisposition. These mechanisms collectively elevate pulmonary artery pressure, leading to right ventricular dysfunction and significantly impacting the patient's quality of life and

Box 3 HAPH patient training and health guidance

Patient training	Health guidance
1. Patients can identify the main symptoms of HAPH, such as dyspnea, fatigue, chest pain, and edema 2. Medication guidance: How to take medication correctly, take it on time and in the right amount, avoid stopping medication or adjusting dosage on your own, identify adverse drug reactions, and communicate with your doctor in a timely manner 3. Self-monitor, learn to use a pulse oximeter, and monitor blood oxygen levels regularly. Record daily symptom changes, such as dyspnea, activity tolerance, weight changes, etc 4. Oxygen therapy guidance, learn to use home oxygen therapy equipment correctly, and understand the adjustment and maintenance of oxygen flow. According to the doctor's recommendations, determine the time and frequency of daily oxygen therapy to ensure adequate oxygen supply	1. Adjust lifestyle and avoid high-intensity exercise. Avoid strenuous exercise and heavy physical labor to prevent excessive burden on the heart and lungs 2. Work and rest reasonably, maintain a regular schedule, and avoid staying up late and overexertion 3. Diet adjustment, the diet should be light and easy to digest, avoid high-salt and high-fat foods, and eat more foods rich in vitamins and minerals 4. Reduce exposure to plateaus and try to avoid going to higher altitudes. If you must go, you should adapt in advance and increase oxygen supply. Go down the mountain regularly, and if conditions permit, return to lower altitudes regularly to relieve the long-term pressure on the body caused by the high altitude 5. Follow up regularly, conduct regular follow-up visits according to the doctor's recommendations, conduct blood oxygen, electrocardiogram and pulmonary function tests, and adjust the treatment plan in a timely manner. If you encounter changes in your condition or uncomfortable symptoms, you should communicate with your doctor in time to avoid delaying treatment 6. Mental health and psychological counseling: Help patients face the disease correctly, maintain an optimistic attitude, and seek help from a psychologist when necessary

survival. Despite notable advancements in HAPH research, its intricate and multifaceted nature continues to pose challenges in comprehending and managing the disease effectively. Treatment strategies for HAPH typically involve drug therapy, oxygen therapy, and lifestyle interventions, and the follow-up health guidance for HAPH patients is also of great significance, see Box 3 for the health guidance. However, achieving the desired effect with a single treatment method can be challenging due to individual differences and the diverse nature of conditions. Therefore, comprehensive treatment management is crucial, by fostering multidisciplinary collaboration and tailoring personalized treatment plans to the patient's specific conditions, the disease can be better controlled and the patient's prognosis can be enhanced.

In clinical research, early diagnosis and timely intervention are crucial in improving the survival rate and quality of life for patients with HAPH. Medical institutions in high-altitude areas should enhance awareness and screening of HAPH, particularly through regular monitoring of high-risk groups. Additionally, medical personnel should undergo relevant training to stay updated on the latest diagnostic and treatment technologies, ensuring the delivery of optimal medical care to patients. In the realm of public health, the prevention and control of HAPH necessitates collaborative actions from both the government and society. There should be an emphasis on enhancing the medical infrastructure in plateau regions to enhance the availability and standard of medical services. Widespread health education initiatives should be implemented to disseminate pertinent information about HAPH and enhance public consciousness regarding disease prevention. Furthermore, it is imperative for the government to establish pertinent policies to bolster research and prevention efforts related to HAPH, as well as to facilitate the advancement and utilization of new pharmaceuticals and treatments.

As a serious chronic disease, HAPH necessitates collaboration among multiple parties for its prevention and treatment. By implementing comprehensive treatment management and multilevel intervention measures, the condition can be effectively controlled, thereby enhancing the patient's quality of life and survival rate. Future research should focus on delving deeper into the pathological mechanism of HAPH, developing more effective diagnosis and treatment methods, and ultimately providing more hope and well-being for patients.

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Declarations

Conflict of interest The authors declare no competing interests.

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