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High-altitude pulmonary hypertension

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ABSTRACT: High-altitude pulmonary hypertension (HAPH) is a specific disease affecting populations that live at high elevations. The prevalence of HAPH among those residing at high altitudes needs to be further defined. Whereas reduction in nitric oxide production may be one mechanism for the development of HAPH, the roles of endothelin-1 and prostaglandin I_2 pathways in the pathogenesis of HAPH deserve further study.

Although some studies have suggested that genetic factors contribute to the pathogenesis of HAPH, data published to date are insufficient for the identification of a significant number of gene polymorphims in HAPH.

The clinical presentation of HAPH is nonspecific. Exertional dyspnoea is the most common symptom and signs related to right heart failure are common in late stages of HAPH. Echocardiography is the most useful screening tool and right heart catheterisation is the gold standard for the diagnosis of HAPH. The ideal management for HAPH is migration to lower altitudes. Phosphodiesterase 5 is an attractive drug target for the treatment of HAPH.

In addition, acetazolamide is a promising therapeutic agent for high-altitude pulmonary hypertension. To date, no evidence has confirmed whether endothelin-receptor antagonists have efficacy in the treatment of high-altitude pulmonary hypertension.

KEYWORDS: High-altitude pulmonary hypertension, hypoxia-inducible factor-1, nitric oxide, phosphodiesterase inhibitors, pulmonary vasoconstriction, right heart catheterisation

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High-altitude pulmonary hypertension (HAPH) due to chronic exposure to high altitude is a designated subset of pulmonary hypertension (PH) according to the third clinical classification of PH, which was approved during a conference in 2003 in Venice, Italy [1].

It is estimated that more than 140 million people live 2,500 m above sea level, and the number of temporary visitors to mountains is close to 40 million [2, 3]. Due to the substantial population exposed to the effects of high altitude, HAPH has become a public health problem in mountainous regions throughout the world. There are three specific locations where high-altitude studies have recently been performed: 1) the Himalayas of Asia; 2) the Andes of South America; and 3) the Rocky Mountains of North America. The present review will focus on the epidemiology, pathophysiology, pathogenesis, clinical characteristics and treatment of HAPH.

DEFINITION

HAPH is a clinical syndrome seen in adults and children residing in high-altitude regions. As chronic mountain syndrome (CMS) is characterised by severe hypoxaemia, excessive polycythaemia and marked PH [4], HAPH is regarded as an important subset of CMS. However, the definition and diagnostic criteria of HAPH remain somewhat vague. According to the 2003 conference on PH, HAPH is classified in the third group of PH (table 1) [1]. Thus, right heart catheterisation is required to establish the diagnosis of HAPH (PH is defined by a mean pulmonary artery pressure ($\bar{P}$pa) of >25 mmHg at rest or >30 mmHg with exercise) [5].

EPIDEMIOLOGY

Although HAPH is not a rare disorder in high-altitude residents and systolic pulmonary pressure can be evaluated easily, PH is infrequently noted in most CMS studies. As a result, the prevalence of HAPH among general highland residents is still unknown.

ALDASHEV *et al.* [6] surveyed the prevalence of HAPH in 741 high-altitude permanent inhabitants in a Kyrgyz population and in 2002 reported that ECG signs of cor pulmonale were presented in 23% of males and 6% of females ($p<0.0001$). In total, 11 subjects (10 males and one female) from this cohort were further studied by right heart catheterisation. The $\bar{P}$pa in this subgroup was 31.6±3.9 mmHg (range 20–64 mmHg). A resting $\bar{P}$pa of >25 mmHg was detected in eight subjects. However, all subjects had a pulmonary vascular resistance of >200 dyn·s·m^{-5} (mean±SD 465±62 dyn·s·m^{-5}, range 283–925 dyn·s·m^{-5}).

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TABLE 1 Revised clinical classification of pulmonary hypertension (PH)

1. Pulmonary arterial hypertension (PAH)
- 1.1. Idiopathic PAH
- 1.2. Familial PAH
- 1.3. Associated with PAH
  - 1.3.1. Collagen vascular disease
  - 1.3.2. Congenital systemic-to-pulmonary shunts
  - 1.3.3. Portal hypertension
  - 1.3.4. HIV infection
  - 1.3.5. Drugs and toxins
  - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
- 1.4. Associated with significant venous or capillary involvement
  - 1.4.1. Pulmonary veno-occlusive disease
  - 1.4.2. Pulmonary capillary haemangiomatosis
- 1.5. Persistent PH of the newborn

2. PH with left heart disease
- 2.1. Left-sided atrial or ventricular heart disease
- 2.2. Left-sided valvular heart disease

3. PH associated with lung diseases and/or hypoxaemia
- 3.1. Chronic obstructive pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Sleep-disordered breathing
- 3.4. Alveolar hypoventilation disorders
- 3.5. Chronic exposure to high altitude
- 3.6. Developmental abnormalities

4. PH due to chronic thrombotic and/or embolic disease
- 4.1. Thromboembolic obstruction of proximal pulmonary arteries
- 4.2. Thromboembolic obstruction of distal pulmonary arteries
- 4.3. Nonthrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscellaneous

Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

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Several studies have shown a prevalence of HAPH between 5 and 18% in the population living at ⩾3,200 m on the Altiplano in South America [7, 8]. WU and GE [9] reported that in the Qinghai Province of China HAPH is more common in children than adults and the enhanced incidence of HAPH with increasing altitude is more pronounced in children than adults. However, fewer HAPH patients were found among both children and adults in a population of Tibetan natives [9]. In contrast, a study by CHEN [10] in Tibet on 300 adult HAPH patients (289 males and 11 females) disclosed evidence of severe PH and enlargement of right or both ventricles as shown by ECG and chest radiographic examination. Furthermore, PH was found to be a common feature of high-altitude heart diseases.

PATHOLOGY

HAPH is characterised by increased pulmonary vascular resistance secondary to hypoxia-induced pulmonary vasoconstriction and vascular remodelling of pulmonary arterioles [11, 12]. The vascular alterations involve all elements of the vessel wall and include endothelial dysfunction, extension of smooth muscle into previously non-muscular vessels and adventitial thickening [13, 14]. Sites of hypoxic pulmonary vasoconstriction are small pulmonary arterioles and veins with a diameter of <900 μm. Venous changes account for ~20% of the total increase in pulmonary vascular resistance caused by hypoxia [7, 8]. The result of these changes is an increased pressure load on the right ventricle leading to reduced exercise capacity and premature death from right ventricular failure. The structural changes in the pulmonary vasculature are due, at least in part, to hypoxia-associated smooth muscle cell proliferation and, together with increased pulmonary vascular tone, represent targets for therapeutic intervention [6].

Histological examination of the pulmonary vessels in high-altitude residents who died from causes other than CMS showed persistence of the typical fetal patterns (thickened media) [15, 16]. The fact that high altitude-induced changes of the pulmonary vasculature and right heart are reversible upon relocation to a lower altitude suggests a rapid remodelling process of the pulmonary vessels in response to changes in atmospheric oxygen content [17]. Moreover, the fact that at high altitude supplemental oxygen significantly decreases pulmonary arterial pressure (P_{pa}), both in acclimatised healthy subjects and long-term high-altitude residents, also supports this remodeling concept [10, 18]. The study by LI and SUI [19] reported autopsy results of 20 adults and 100 infants from Tibet who had died of HAPH. The major findings included dilatation of the pulmonary artery trunk, atheromas and thrombosis of the pulmonary artery, and hypertrophy and dilation of the right ventricle and right atrium. Hypertrophy of both ventricles was also found in some cases. Compared with the normal age-matched controls, the ratio of right to left ventricular weight of these patients was significantly greater and the weight of the right ventricle even exceeded the left ventricle in some cases. Severe medial hypertrophy of the small pulmonary arteries with crenation of the elastic laminae was the most significant histological finding in the pulmonary vasculature.

PATHOPHYSIOLOGY

Sustained alveolar hypoxia, such as that experienced by high-altitude residents, has a marked physiological impact on the pulmonary vasculature. The haemodynamic outcome (*i.e.* increased P_{pa}) is due to enhanced pulmonary vasoconstriction and pulmonary vascular remodelling, both of which cause reduction of the vascular lumen diameter and an increase in pulmonary vascular resistance [11, 12]. In rats exposed to hypoxia, pre-capillary vessels of a diameter of ~25 mm, which normally do not have smooth muscle cells, begin to generate from adventitial fibroblasts within 24 h [20]. Light microscopic examination of non-muscular arterioles after exposure to hypoxia shows that smooth muscle begins to appear by day 2 at simulated altitude, with the proportion of muscularised arterioles corresponding to the increasing P_{pa} [21, 22]. Interestingly, these previous studies show that after returning to normoxia, smooth muscle cells persisted in normally non-muscularised arterioles, suggesting that the histological changes may persist for a very long time after chronic exposure to hypoxia. If confirmed in humans, these findings suggest that hypoxia-associated smooth muscle proliferation in originally weakly muscularised arterioles and normally non-muscular pulmonary vessels is likely to be a major pathophysiological mechanism for the development of HAPH.

PATHOGENESIS

The biochemical mechanisms underlying the pathogenesis of HAPH are poorly understood, but a reduction in nitric oxide (NO) production is thought to play a role [23]. Animal studies showed that the absence of endothelial NO synthase increased susceptibility to HAPH [24]. ANAND *et al.* [25] demonstrated that inhaled NO can cause an acute decrease in P_{pa}, intrapulmonary shunting and improvement in oxygenation in high-altitude pulmonary oedema patients. The roles of endothelin-1 and prostaglandin I_2 pathways in the pathogenesis of HAPH are still not well characterised.

In the pulmonary vasculature, it appears that transmembrane ion flux plays an important role in controlling the cellular processes that underlie both vasoconstriction and medial hypertrophy and hyperplasia during hypoxic exposure [26]. Alteration in the transport of K^+ and Ca^{2+} through their respective ion channels modulates these processes by affecting cell volume, membrane potential, cytosolic Ca^{2+} concentration, gene transcription, apoptosis and cell-cycle progression. Precisely how K^+ and Ca^{2+} channels ''sense'' changes in oxygen tension or how their activity and expression somehow ''adapt'' at higher altitudes is unclear. Although pulmonary physiologists are attempting to define this mechanism, it is becoming increasingly apparent that ion channels themselves are probably not the actual oxygen sensors.

GENETICS

It is possible that individuals who develop high-altitude PH share common and, as yet, unidentified genes that influence the pulmonary arteriolar and/or venous response to hypoxia and the generation of smooth muscle cells from adventitial fibroblasts in weakly and non-muscularised pulmonary vessels. Previous studies have shown that Tibetan-native Chinese, compared to Han Chinese or South American high-altitude natives, have a remarkable lack of muscularisation of pulmonary arteries, and lower hypoxic pulmonary vasoconstrictive response and haemoglobin concentration [27]. This suggests that Tibetans' protection from high altitude-related illnesses might be due to genetic factors. LEÓN-VELARDE and MEJÍA [28] summarised the available data on genes known to be regulated by hypoxia-inducible factor-1 and/or by hypoxia that have been studied in populations from high-altitude regions suffering from HAPH. Even though some alleles are more prevalent (G allele of endothelial NO synthase polymorphism Glu298Asp in Sherpas and angiotensin-converting enzyme (ACE)I allele in HAPH Kyrgyz) or less prevalent (ACE D allele in high-altitude Andeans) in the different high-altitude populations, data published to date are inconclusive regarding these gene polymorphisms in HAPH [28].

CLINICAL PRESENTATIONS

Symptoms

Polycythaemia, hypoxaemia and pulmonary arterial hypertension (PAH) are principal characteristics of CMS. It is highly intriguing that PAH has not been quantified as part of the proposed definition of CMS [29]. At an early stage, PH may be asymptomatic but, as the condition progresses, exertional dyspnoea becomes the most frequent presenting symptom. Moreover, fatigue, weakness, anginal chest pain, syncope and exercise intolerance are also common complaints. In addition to these symptoms of PH, HAPH patients may also manifest common symptoms of CMS, such as headache, dizziness, insomnia, cognitive dysfunction, somnolence, slowed mental function, confusion and impaired memory [30].

Physical examination

Episodes suggestive of right heart failure with dyspnoea, cough, turgid jugular veins and peripheral oedema follow the initial symptoms within a few years in Han Chinese subjects [4, 31], but are rare in high-altitude residents in the Andes [32]. In both populations, marked cyanosis of the face and fingers, clubbing of the digits, hepatomegaly and ascites may be present in the late stage of the disease.

Electrocardiogram

Indices of right ventricular hypertrophy can be seen on ECG including changes in the mean QRS electrical axis in the frontal plane (standard leads I, II and III) exceeding +90°.

Pulmonary function test

Patients with HAPH are usually more hypoxaemic than normal high-altitude residents, in part because of hypoventilation during both awake and sleep states. Compared with residents living at sea level, it has been found that both healthy residents at high altitude and patients with HAPH present a decreased ventilatory response to hypoxia, with the difference between those with and without HAPH not being statistically significant [33]. However, compared with healthy high-altitude residents, patients with HAPH present higher end-tidal carbon dioxide tension and lower end-tidal oxygen tension, suggesting a lower level of alveolar ventilation rather than a hypoxic ventilatory response in these subjects [33, 34]. Thus, from the results of these studies, it may be concluded that a lower level of alveolar ventilation rather than a reduced peripheral chemosensitivity to hypoxia is the primary mechanism leading to hypoxaemia.

Chest radiography

Enlargement of the heart, dilatation of the pulmonary trunk and general dilatation of the small lung vessels were found on chest radiography and reported in Han Chinese and South Americans. Kearly's B lines are characteristically absent in HAPH patients [4]. These symptoms suggest that congestive right heart failure is associated with excessively elevated PAP in both populations.

Echocardiography

Echocardiography can provide both estimates of P_{pa} and an assessment of cardiac structure and function [35]. These features justify its application as the most commonly used screening tool in assessing patients with suspected HAPH. Systolic P_{pa} is calculated by adding the estimated right atrial pressure to the pressure gradient between the right ventricle and the right atrium, RV and RA, respectively, (ΔP-RV/RA) using the modified Bernouilli equation, as follows:

$$\Delta\text{P-RV/RA} = 4\text{V}^2 \quad (1)$$

where V is the peak velocity of the regurgitant jet across the tricuspid valve and Δ indicates change.

Right heart catheterisation

For the purposes of confirming the diagnosis, as well as excluding PH due to other causes, right heart catheterisation

measure of P_{pa} is recommended [35]. Pulmonary haemodynamic measurements performed in children and young adults show persistence of elevated P_{pa} at high altitude for weeks, months or years [36]. Performance of right heart catheterisation was reported in Han Chinese subjects who developed HAPH after residing in Lhasa at an elevation 3,658 m for 11–36 yrs, as well as in Andes natives residing at an elevation of ~4,300 m [32]. The haemodynamic data showed the $\bar{P}_{pa}$ averaged 45 mmHg in Andes natives and 40 mmHg in Han Chinese subjects. In all subjects, right atrial pressure, pulmonary artery occlusion pressure and cardiac output were normal. Although right heart catheterisation is the gold standard for the diagnosis of PH, its use in the diagnosis of HAPH is quite limited and should be adopted more widely in the future by clinicians.

TREATMENTS

The ideal management for HAPH is migration to low altitude. However, for patients who choose to remain at high altitude, other means of reducing PH may be attempted, although their efficacy has not been fully established.

A number of treatments including oxygen supplementation, calcium channel blockers (such as nifedipine), NO inhalation, prostacyclins and endothelin-receptor antagonists, as well as phosphodiesterase inhibitors, have been demonstrated to decrease hypoxaemia, PH and the alveolar–arterial gradient in PAH. However, the efficacy of these treatments for HAPH needs to be further evaluated.

NO has vasorelaxant and antiproliferative effects that are mediated by cyclic guanosine monophosphate (cGMP). cGMP is hydrolysed by phosphodiesterases (PDEs). PDE5 is the major PDE subtype present in pulmonary vasculature and is more abundant in the lungs than in other tissues [37]. This abundance of PDE5 in the lungs provides a mechanism for relatively selective pulmonary vasodilatation with little systemic hypotension. Agents with PDE5 inhibitory activity reduce P_{pa} in animal models [38]. ALDASHEV *et al.* [39] studied the effects of sildenafil in 14 HAPH patients and reported a reduction in $\bar{P}_{pa}$, with an improvement in 6-min walk distance and an increase in cardiac index after 3 months. Therefore, PDE5 is an attractive drug target for the treatment of HAPH. Long-term treatment with a PDE5 inhibitor, such as sildenafil, maybe a promising therapy for HAPH.

Although endothelin-receptor antagonists have been proven to reduce P_{pa} and increase exercise capacity in patients with PAH, their effects on exercise capacity at altitude are unknown. Recently, SEHEULT *et al.* [40] demonstrated that bosentan therapy initiated 5 days prior to ascent to high altitude did not improve exercise capacity or reduce systolic pulmonary arterial hypertension, and worsened arterial oxygen saturation measured by pulse oximetry during high-intensity exercise at altitude.

A number of studies have emphasised the mechanisms by which acetazolamide and angiotensin-converting enzyme inhibitors may be effective agents for the treatment of high-altitude pulmonary hypertension. RICHALET *et al.* [41] demonstrated that acetazolamide reduces hypoventilation, improves pulmonary circulation and decreases erythropoiesis. Its use as a chronic treatment for high-altitude pulmonary hypertension has been shown to be efficacious and safe [42]. The low cost of acetazolamide may allow for wide adoption with a considerable positive impact on public health in high-altitude regions. The study of angiotensin-converting enzyme inhibitors in the treatment of high-altitude pulmonary hypertension is still ongoing.

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