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High-altitude Pulmonary Hypertension: an Update on Disease Pathogenesis and Management

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Abstract: High-altitude pulmonary hypertension (HAPH) affects individuals residing at altitudes of 2,500 meters and higher. Numerous pathogenic variables play a role in disease inception and progression and include low oxygen concentration in inspired air, vasculopathy, and metabolic abnormalities. Since HAPH affects only some people living at high altitude genetic factors play a significant role in its pathogenesis.

The clinical presentation of HAPH is nonspecific and includes fatigue, shortness of breath, cognitive deficits, cough, and in advanced cases hepatosplenomegaly and overt right-sided heart failure. A thorough history is important and should include a search for additional risk factors for lung disease and pulmonary hypertension (PH) such as smoking, indoor air pollution, left-sided cardiac disease and sleep disordered breathing. Twelve-lead electrocardiogram, chest X-ray and echocardiography can be used as screening tools. A definitive diagnosis should be made with right-sided heart catheterization using a modified mean pulmonary artery pressure of at least 30 mm Hg, differing from the 25 mm Hg used for other types of PH.

Treatment of HAPH includes descent to a lower altitude whenever possible, oxygen therapy and the use of medications such as endothelin receptor antagonists, phosphodiesterase 5 blockers, fasudil and acetazolamide. Some recent evidence suggests that iron supplementation may also be beneficial. However, it is important to note that the scientific literature lacks long-term randomized controlled data on the pharmacologic treatment of HAPH. Thus, an individualized approach to treatment and informing the patients regarding the benefits and risks of the selected treatment regimen are essential.

Keywords: Altitude physiology, cardiac failure, epidemiology, treatment.

1. INTRODUCTION

Pulmonary hypertension (PH) is a group of disorders generally characterized by a mean pulmonary arterial pressure ≥ 25 mm Hg on right heart catheterization [1 - 3]. The most recent PH classification includes five main groups shown in Table 1. The association of PH with other medical disorders has a worse prognosis. For example, the presence of PH in chronic obstructive pulmonary disease (COPD) is linked to greater morbidity and mortality [4].

High-altitude pulmonary hypertension (HAPH) is included in the third of these groups according to the latest classification of PH [1]. It is known that more than 140 million people permanently reside at high altitudes and more than 40 million people visit these areas for recreational and other reasons [6]. Indeed, some lowland individuals develop acute mountain sickness every year due to rapid ascent and the decrease in partial pressure of oxygen [7].

The goal of this article is to review our current understanding of HAPH. First, the pathogenesis of HAPH will be discussed, including the role of hypoxia, genetics and other factors that play a role in the development of this disease. Second, the epidemiology of HAPH will be reviewed. Third, we will discuss the clinical presentation and symptomatology of HAPH. Fourth, the diagnostic work-up of patients with HAPH will be reviewed. Finally, we will

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discuss the therapeutic options and management of patients with HAPH.

2. SEARCH STRATEGY

We searched PubMed/Medline, Scopus, Embase and Web of Science for articles focused on high-altitude pulmonary hypertension published from 1950 to January 2015. The search terms were: high-altitude pulmonary hypertension, chronic mountain sickness, mountain sickness, cardiac mountain sickness, Monge disease and the combination of these. The reference lists of the identified articles were further screened for potentially relevant articles that may have been overlooked by the electronic search. The search methodology was adapted from the scientific search guidelines published in 2011 [5].

3. PATHOGENESIS OF HAPH

It is well known that high altitude areas have a lower oxygen concentration compared to lowland territories [8]. Indeed, research data show that a hypoxic stimulus leads to pulmonary vasoconstriction and an increase in pulmonary vascular resistance [9]. This physiologic response is an important phenomenon aiming to reduce the perfusion of poorly ventilated lung areas and redistribute more blood flow to better-oxygenated zones. Hypoxic stimuli also lead to vascular remodeling at the level of small pulmonary arteries and veins, which are normally devoid of smooth muscle cells [9, 10]. However, hypoxia appears to stimulate the proliferation of smooth muscle cells from the local myofibroblasts [9 - 4]. It is interesting to note that these vascular changes persist even after return to normoxia, suggesting that these morphologic changes play an important role in the perpetuation of elevated pulmonary artery pressure.

On a molecular level, hypoxia alters the activity of ion channels. More specifically, hypoxia downregulates the activity of potassium channels and modulates the activity of calcium channels, leading to an increase in intracellular calcium [15]. These changes in turn augment smooth muscle cell proliferation, reduce the apoptosis of smooth muscle cells and alter the activity of pulmonary endothelial cells, favoring the production of vasoconstrictive substances such as endothelin, thromboxane A₂ and others [16 - 20].

Nitric oxide (NO) is a key vasodilator of the pulmonary circulation and its decreased availability is believed to play a major role in the development of PH [21]. It has been shown by Anand that inhaled NO can mitigate pulmonary vascular resistance in patients with acute mountain sickness in the form of high-altitude pulmonary edema [22]. Furthermore, certain medications used in the management of PH target the bioavailability of NO as will be discussed in the treatment section. It is interesting to note here that some populations living at high altitude for a long time have a lower prevalence of HAPH and other high-altitude-related diseases. For example, native Tibetans have higher pulmonary NO concentrations than other populations which might explain a low prevalence of HAPH [23 - 27]. In a recent study, Siques *et al.* demonstrated that continuous hypoxia results in both the decreased synthesis and bioavailability of NO [28]. Furthermore, α 1-A680T Variant in GUCY1A3 (guanylate cyclase) may be protective against the development of HAPH through increase in cellular NO [29].

Scientific data suggest that genetics plays a role in the susceptibility to HAPH. For example, the Sherpa ethnic group living in Nepal has a Glu 298Asp polymorphism of the G allele of the NO synthase gene [30]. The role of angiotensin converting enzyme (ACE) polymorphisms has also been studied. Aldashev *et al.* studied ACE genotyping among 212 adult Kyrgyz lowlanders and 78 adult male highlanders [31, 32]. These researchers showed that the I allele of ACE was associated with the presence of HAPH. The results of this study were interesting since the I allele is associated with a reduced level of ACE activity, which should have a vasodilatory effect on the pulmonary circulation due to the reduced availability of angiotensin II. These researchers speculated that the I allele of ACE may endure greater physical endurance, which in turn may lead to augmented cardiac output and pulmonary artery pressure; alternatively, the association between ACE and HAPH could be explained by the proximity of the ACE gene to a HAPH susceptibility locus. Finally, the susceptibility of the Kyrgyz population to HAPH in their study was associated with hyperreactivity to acute hypoxia. For a more detailed discussion on genetic susceptibility to HAPH and other high-altitude diseases the reader is referred to a well-written review article [30].

It is important to bear in mind that other factors may contribute to the development of elevated PH in people living at high altitude. For example, premenopausal women have a lower burden of HAPH compared to men [33]. This observation may be explained by the stimulatory effects of female sex hormones on ventilatory drive. Indeed, the native Tibetan population has augmented ventilation, which is believed to be protective against the development of HAPH.

Other factors that can detrimentally affect pulmonary artery pressure and pulmonary health include sleep disordered

breathing [34, 35], indoor air pollution [36], smoking [37], iron deficiency [38] and erythrocytosis with increased blood viscosity [39].

In summary, hypoxic stimuli lead to an increase in pulmonary arterial vasoconstriction and vascular remodeling through the alteration of ion channel activity. Vascular remodeling includes the proliferation of smooth muscle cells in pulmonary vessels that are normally devoid of them and decreased apoptosis of these cells. Moreover, it also modulates the biochemical activity of pulmonary endothelium with a shift towards the production of substances such as endothelin-1. The role of genetic predisposition seems to be essential for the development of disease, but is not entirely understood at this time. Other factors and comorbidities may also play some role in selected circumstances.

4. EPIDEMIOLOGY OF HAPH

As mentioned above, about 140 million people permanently live at high altitude, which is generally defined as being at least 2500 meters above sea level [6, 7]. Current scientific data on the prevalence of HAPH are scarce. Nevertheless, several studies have attempted to investigate the burden of HAPH in at-risk populations.

Aldashev *et al.* screened 741 high-altitude residents *via* electrocardiogram (ECG) for the presence of ECG findings of right heart hypertrophy and involvement [32]. They demonstrated that 23% of men and 6% of women had ECG evidence of right heart involvement. Eleven patients further underwent right heart catheterization, and a resting mean pulmonary artery pressure >25 mm Hg was found in eight of these. In a later study, Aldashev *et al.* screened 689 high-altitude residents (313 men) with ECG for the presence of right ventricular involvement [40]. The ECG criteria for right ventricular hypertrophy were met in 188 subjects (27%) of whom 113 were men. Later, right cardiac catheterization was performed in 44 individuals with ECG evidence of right ventricular hypertrophy. It was found that 29 patients (25 men) who underwent right cardiac catheterization had a mean pulmonary artery pressure >25 mm Hg. It was estimated that the prevalence of HAPH was 18% in their study. However, it is essential to bear in mind that the sensitivity of ECG for the detection of right ventricular enlargement as a marker of HAPH is quite low, at around 20% [41].

Studies from South America have demonstrated a prevalence of HAPH ranging from 5 to 18% [9, 42]. Thus, based on current scientific literature we can assume that the rough prevalence of HAPH ranges from 5 to 18% in populations at risk and is more common in men. In a recent study by Negi *et al.* demonstrated HAPH prevalence of 3.23% among natives of Spiti Valley, India [43].

Table 1. Classification of PH.

Group	Etiologies
Group 1.	Idiopathic, heritable, connective tissue disease, HIV infection, portopulmonary hypertension, congenital heart disease, drug/toxin induced, chronic hemolytic anemia, schistosomiasis, persistent PH of the newborn, pulmonary venoocclusive disease and pulmonary capillary hemangiomatosis.
Group 2. PH owing to left heart disease	Systolic and diastolic dysfunction, mitral and aortic valve diseases
Group 3. Pulmonary hypertension owing to lung diseases and/or hypoxia	High-altitude pulmonary hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep disordered breathing <i>etc.</i>
Group 4. Chronic Thromboembolic pulmonary hypertension	Unresolved fibrin thromboembolization to the pulmonary arteries.
Group 5. Pulmonary hypertension with unclear multifactorial mechanisms	Myeloproliferative disorders, splenectomy, pulmonary vasculitis, neurofibromatosis, thyroid disorders <i>etc.</i>

5. CLINICAL PRESENTATION OF HAPH

The clinical presentation of PH is nonspecific, and patients typically present with exertional symptoms such as progressive dyspnea, chest pain/discomfort, and in advanced cases dizziness and syncope [1]. Cough, hemoptysis, fatigue, and lower extremity pitting edema are also common presenting features. It is also important to bear in mind that patients with HAPH may have other non-specific symptoms such as fatigue, headaches and cognitive impairment [44].

Physical examination can be very helpful in signaling problems in the pulmonary circulation. An early manifestation is an increase in the intensity of the second pulmonic sound (P2), but as the disease progresses, the right ventricle enlarges so that an impulse or heave can be appreciated in the left lower sternal border. The tricuspid valve becomes more incompetent as the RV enlarges, and a holosystolic murmur indicative of tricuspid regurgitation becomes audible in the left and right lower sternal borders. The onset of RV failure leads to jugular venous stenosis, hepatojugular reflux, peripheral edema, liver and spleen enlargement as well as ascites [2]. These are not specific for

isolated right ventricular failure and are also commonly seen with left ventricular dysfunction. During physical examination, it is essential to search for signs of systemic autoimmune diseases (particularly systemic sclerosis) such as joint pains, skin thickening, malar rash, telangiectasia, and Raynaud's phenomenon in order to detect other potential etiologies for elevated pulmonary artery pressure [1, 44, 45].

6. DIAGNOSTIC WORK-UP OF HAPH

It is important to consider the diagnosis of PH in patients with shortness of breath, syncope, fatigue, peripheral edema, abdominal discomfort and hepatomegaly. The symptoms and signs mentioned above are nonspecific for PH. Physical examination is essential and should focus on the signs presented in the previous section. It is also important to emphasize that history and physical examination should seek alternative or additional risk factors for PH in people residing at high altitudes such as smoking, presence of sleep disordered breathing, autoimmune disease *etc.* Furthermore, the diagnosis of HAPH requires residence at an altitude of at least 2500 meters above sea level [44].

Several instrumental tests can be of help in evaluating patients with the aforementioned complaints and physical signs. Twelve-lead electrocardiogram (ECG) is a relatively inexpensive diagnostic tool that can also assist in detecting other potential explanations for the patients' presentation. ECG may reveal "p" pulmonale consisting of tall P waves (≥ 3 mm) in the inferior leads, right axis deviation, or right bundle branch block and R to S ratio > 1 in lead V1, indicative of right ventricular hypertrophy. ST depression in leads V1 to V3 suggests right ventricular strain in combination with other findings. However, these findings were shown to have limited sensitivity for diagnosing PH, especially in patients with mild PH [41, 46], and are of limited prognostic value [46].

Echocardiography in patients with PH may show an increase in pulmonary artery pressure, as well as enlargement of right atrium and ventricle. It also provides important information on left heart function. Despite having much greater sensitivity and specificity for PH than the ECG and CXR, the cardiac echo may under or overestimate the degree of pulmonary artery pressure [47]. It is important to note that ECG combined with echocardiographic assessment may be used for the screening of HAPH given their noninvasive nature, as shown by Kojonazarov *et al.* in a study of Kyrgyz highlanders [48].

Chest X-ray (CXR) is an important test for evaluating patients presenting with shortness of breath, chest pain, and other respiratory-related symptoms, as PH is one of many conditions that can present with these symptoms (such as pulmonary hyperinflation secondary to chronic obstructive pulmonary disease). In PH, the CXR may be completely normal but is apt to show evidence of RV or PA enlargement and prominence of pulmonary vasculature in advanced cases. However, the utility of CXR in diagnosing PH is limited due to its lack of sensitivity.

Pulmonary function tests (PFT) are important mostly to exclude other potential causes of PH (such as chronic obstructive pulmonary disease and interstitial lung diseases) [2, 3].

Nuclear ventilation perfusion (V/Q) scans are typically performed in order to exclude chronic thromboembolic pulmonary hypertension (CTEPH) [2]. V/Q scans can show large ventilation perfusion mismatch suggestive of CTEPH. It is important to be aware of the limitations of V/Q scans, which include decreased sensitivity and specificity in patients with underlying pulmonary disease, and overall low specificity, since other pathologies may give similar findings. Due to the limited specificity of V/Q scans, patients with positive findings typically undergo further imaging studies to better quantify disease severity and exclude alternative diagnoses. As long as renal function is acceptable, computed tomography-pulmonary angiography (CT-PA) is usually performed next in cases of suggestive V/Q scans, since it has greater specificity than V/Q scans and can help exclude other diseases.

Pulmonary angiography (PA) and right heart catheterization is the mainstay of diagnosis confirmation and disease prognostication. Measurement of mPAP at rest and mean pulmonary capillary wedge pressure (mPCWP) is performed during right heart catheterization. PH is diagnosed when mPAP during rest ≥ 25 mmHg and mPCWP < 15 mmHg [1]. However, it is important to bear in mind that mPAP of > 30 mm Hg and systolic PAP of > 50 mm Hg should be used as diagnostic criteria for HPAH [44]. The measurement of mPCWP is important since PH secondary to left heart disease is essentially ruled out at values less than 15 mmHg [1]. However, mPCWP > 15 may be secondary to dilation of pulmonary arteries and in such cases, it is essential to measure left ventricular end diastolic pressure. As described earlier it is important to seek additional or alternative etiologies for elevated PAP in patients residing at high altitudes since their presence excludes HAPH [44]. Furthermore, management of elevated PAP can differ from that of HAPH itself as, for example, in the presence of mitral stenosis complicated by the development of PH.

In summary, it is essential to exclude PH secondary to left-sided cardiac disease, PH secondary to pulmonary

disease, CTEPH, and other etiologies in appropriate clinical scenarios (such as portopulmonary hypertension and PH secondary to sickle cell disease) before attributing the etiology to HPAH. Furthermore, right heart catheterization should be performed at the altitude of residence, which is not always technically feasible. It is important to bear in mind that diagnosis of HAPH requires mPAP of more than 30 mm Hg or systolic PAP of more than 50 mm Hg on right heart catheterization [44].

7. TREATMENT OF HAPH

The scientific literature on the topic of management of HAPH is limited to a few randomized trials. It is important to bear in mind that whenever possible it is reasonable to advise migration to lower altitudes. Sime *et al.* showed that high-altitude residents showed normalization of mPAP after 2 years of living at low altitude [49]. It is interesting to note that mPAP increased upon return to high altitude. Fried and Reid also demonstrated this phenomenon following two days of descent to low altitude [50].

It is well known that NO is an essential bioactive chemical and is implicated in the pathogenesis of various forms of PH, including HAPH. Phosphodiesterase type 5 (PDE-5) isoenzyme is a known factor that degrades NO *in vivo*. Medications inhibiting PDE-5 such as sildenafil, tadalafil and others have been shown to be beneficial for patients with HAPH. Richalet *et al.* studied 12 male patients and exposed them to an altitude of 4,350 meters for 6 days [51]. The subjects were randomly assigned to placebo and sildenafil. They showed that subjects assigned to sildenafil had a greater partial pressure of oxygen, a lower difference in oxygen levels between the alveolar and arterial compartments and greater maximal oxygen consumption. In another study, Aldashev *et al.* randomized 22 individuals with HAPH to placebo and sildenafil for 12 weeks in a double-blind fashion [40]. This group showed that sildenafil reduced mPAP, improved physical endurance and had a minimal effect on systemic blood pressure. In a recent meta-analysis Xu *et al.* concluded that sildenafil reduces mPAP, but has no major effects on oxygen saturation and heart rate [52].

Endothelin receptor blockers such as bosentan are used successfully in the management of PAH. In a recent study Seheult *et al.* studied eight patients who were exposed to an altitude of 3,800 meters and randomized them to bosentan and placebo in a double-blind methodology [53]. Bosentan was started 5 days prior to ascent. Unfortunately, bosentan was not shown to reduce mPAP or increase exercise capacity, and actually worsened oxygen saturation. However, a later study by Kojonazarov *et al.*, who enrolled high-altitude residents with HAPH, showed that patients with HAPH have higher levels of endothelin as well as that bosentan therapy reduced pulmonary artery systolic pressure more than oxygen administration [54].

Acetazolamide is a carbonic anhydrase inhibitor and weak diuretic that is a key agent used in the prevention of high-altitude sickness [55]. In a recent study, Richalet *et al.* studied the utility of acetazolamide in the management of chronic altitude sickness [56]. In their study acetazolamide increased nocturnal oxygen saturation and led to a reduction in secondary polycythemia. Moreover, it was shown that acetazolamide reduced pulmonary vascular resistance. Given its minimal side effect profile acetazolamide can be used in patients with chronic mountain sickness and possibly HAPH.

Smith *et al.* aimed to study an interesting hypothesis on iron availability and HAPH [57]. These researchers enrolled two groups of individuals: first 22 healthy subjects normally residing at sea level were exposed to an altitude of 4,340 meters and received intravenous iron sucrose on the third day of stay at high altitude. The second group included 11 men usually residing at high altitude who had chronic mountain sickness and who underwent staged isovolemic venesection of 2 liters of blood. It is interesting to note that iron infusion was associated with reduced pulmonary artery systolic pressure in sea-level residents, whereas venesection was associated with increased pulmonary artery systolic pressure in high-altitude residents. However, iron infusion did not improve pulmonary artery systolic pressure in their study. The researchers concluded that the role of iron may be more complex than believed in the pathogenesis of chronic mountain sickness and HAPH, and avoidance of iron deficiency should be an aim in patients with HAPH.

Kojonazarov *et al.* studied a Rho A/Rho kinase inhibitor fasudil in a double-blind randomized study involving 19 patients with HAPH [58]. It was shown that fasudil beneficially decreased pulmonary artery systolic pressure compared to placebo, was well tolerated and had no effects on systemic blood pressure.

In conclusion, no long-term data are available on the management of HAPH. Ideally, all patients with HAPH should be advised to descend to a lower altitude. The limitations of the data on pharmacological correction of HAPH should be discussed with every patient with HAPH and an informed decision should be reached. The cost of the medications should be kept in mind since a significant percent of high-altitude residents reside in low-income countries and hence,

may not be able to afford them.

CONCLUSION

HAPH is a common disease afflicting individuals living at high altitudes yet this is an understudied disorder. Studies should further elaborate the pathobiology of this condition since many people residing at high altitude do not have this disorder. A better understanding of the disease pathogenesis may translate into newer therapeutic targets and treatments for this condition.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

- [1] Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54(1)(Suppl.): S43-54. [<http://dx.doi.org/10.1016/j.jacc.2009.04.012>] [PMID: 19555858]
- [2] Mirrakhimov AE, Hill NS. Primary antiphospholipid syndrome and pulmonary hypertension. *Curr Pharm Des* 2014; 20(4): 545-51. [<http://dx.doi.org/10.2174/138161282004140213125951>] [PMID: 23565637]
- [3] Mirrakhimov AE, Ali AM, Barbaryan A, Prueksaritanond S. Human immunodeficiency virus and pulmonary arterial hypertension 2013. [<http://dx.doi.org/10.1155/2013/903454>]
- [4] Oswald-Mammosser M, Weitzenblum E, Quoix E, *et al.* Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest* 1995; 107(5): 1193-8. [<http://dx.doi.org/10.1378/chest.107.5.1193>] [PMID: 7750305]
- [5] Gasparyan AY, Ayzvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. *Rheumatol Int* 2011; 31(11): 1409-17. [<http://dx.doi.org/10.1007/s00296-011-1999-3>] [PMID: 21800117]
- [6] West JB, Schoene RB, Luks AM, Milledge JS. High altitude medicine and physiology. 5th ed., London: CRC Press 2012. [<http://dx.doi.org/10.1201/b13633>]
- [7] Bärtsch P, Swenson ER. Clinical practice: Acute high-altitude illnesses. *N Engl J Med* 2013; 368(24): 2294-302. [<http://dx.doi.org/10.1056/NEJMc1214870>] [PMID: 23758234]
- [8] Scoggin CH, Hyers TM, Reeves JT, Grover RF. High-altitude pulmonary edema in the children and young adults of Leadville, Colorado. *N Engl J Med* 1977; 297(23): 1269-72. [<http://dx.doi.org/10.1056/NEJM197712082972309>] [PMID: 917073]
- [9] Hakim TS, Michel RP, Minami H, Chang HK. Site of pulmonary hypoxic vasoconstriction studied with arterial and venous occlusion. *J Appl Physiol* 1983; 54(5): 1298-302. [PMID: 6863090]
- [10] Sobin SS, Tremer HM, Hardy JD, Chiodi HP. Changes in arteriole in acute and chronic hypoxic pulmonary hypertension and recovery in rat. *J Appl Physiol* 1983; 55(5): 1445-55. [PMID: 6643182]
- [11] Rabinovitch M, Konstam MA, Gamble WJ, *et al.* Changes in pulmonary blood flow affect vascular response to chronic hypoxia in rats. *Circ Res* 1983; 52(4): 432-41. [<http://dx.doi.org/10.1161/01.RES.52.4.432>] [PMID: 6831659]
- [12] Heath D, Smith P, Rios Dalenz J, Williams D, Harris P. Small pulmonary arteries in some natives of La Paz, Bolivia. *Thorax* 1981; 36(8): 599-604. [<http://dx.doi.org/10.1136/thx.36.8.599>] [PMID: 7314035]
- [13] Heath D, Williams D, Rios-Dalenz J, Calderon M, Gosney J. Small pulmonary arterial vessels of Aymara Indians from the Bolivian Andes. *Histopathology* 1990; 16(6): 565-71. [<http://dx.doi.org/10.1111/j.1365-2559.1990.tb01161.x>] [PMID: 2376399]
- [14] Pak O, Aldashev A, Welsh D, Peacock A. The effects of hypoxia on the cells of the pulmonary vasculature. *Eur Respir J* 2007; 30(2): 364-72. [<http://dx.doi.org/10.1183/09031936.00128706>] [PMID: 17666559]
- [15] Remillard CV, Yuan JX. High altitude pulmonary hypertension: role of K⁺ and Ca²⁺ channels. *High Alt Med Biol* 2005; 6(2): 133-46. [<http://dx.doi.org/10.1089/ham.2005.6.133>] [PMID: 16060848]
- [16] Burg ED, Remillard CV, Yuan JX. K⁺ channels in apoptosis. *J Membr Biol* 2006; 209(1): 3-20.

- [http://dx.doi.org/10.1007/s00232-005-0838-4] [PMID: 16685597]
- [17] Platoshyn O, Brevnova EE, Burg ED, Yu Y, Remillard CV, Yuan JX. Acute hypoxia selectively inhibits KCNA5 channels in pulmonary artery smooth muscle cells. *Am J Physiol Cell Physiol* 2006; 290(3): C907-16. [http://dx.doi.org/10.1152/ajpcell.00028.2005] [PMID: 16236819]
- [18] Firth AL, Remillard CV, Platoshyn O, Fantozzi I, Ko EA, Yuan JX. Functional ion channels in human pulmonary artery smooth muscle cells: Voltage-dependent cation channels. *Pulm Circ* 2011; 1(1): 48-71. [http://dx.doi.org/10.4103/2045-8932.78103] [PMID: 21927714]
- [19] Berger MM, Dehnert C, Bailey DM, *et al.* Transpulmonary plasma ET-1 and nitrite differences in high altitude pulmonary hypertension. *High Alt Med Biol* 2009; 10(1): 17-24. [http://dx.doi.org/10.1089/ham.2008.1053] [PMID: 19326597]
- [20] Sylvester JT, Shimoda LA, Aaronson PI, Ward JP. Hypoxic pulmonary vasoconstriction. *Physiol Rev* 2012; 92(1): 367-520. [http://dx.doi.org/10.1152/physrev.00041.2010] [PMID: 22298659]
- [21] Klinger JR, Abman SH, Gladwin MT. Nitric oxide deficiency and endothelial dysfunction in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2013; 188(6): 639-46. [http://dx.doi.org/10.1164/rccm.201304-0686PP] [PMID: 23822809]
- [22] Anand IS, Prasad BA, Chugh SS, *et al.* Effects of inhaled nitric oxide and oxygen in high-altitude pulmonary edema. *Circulation* 1998; 98(22): 2441-5. [http://dx.doi.org/10.1161/01.CIR.98.22.2441] [PMID: 9832490]
- [23] Beall CM, Laskowski D, Strohl KP, *et al.* Pulmonary nitric oxide in mountain dwellers. *Nature* 2001; 414(6862): 411-2. [http://dx.doi.org/10.1038/35106641] [PMID: 11719794]
- [24] Hoit BD, Dalton ND, Erzurum SC, Laskowski D, Strohl KP, Beall CM. Nitric oxide and cardiopulmonary hemodynamics in Tibetan highlanders. *J Appl Physiol* 2005; 99(5): 1796-801. [http://dx.doi.org/10.1152/jappphysiol.00205.2005] [PMID: 16024527]
- [25] Beall CM, Laskowski D, Erzurum SC. Nitric oxide in adaptation to altitude. *Free Radic Biol Med* 2012; 52(7): 1123-34. [http://dx.doi.org/10.1016/j.freeradbiomed.2011.12.028] [PMID: 22300645]
- [26] Strohl KP. Lessons in hypoxic adaptation from high-altitude populations. *Sleep Breath* 2008; 12(2): 115-21. [http://dx.doi.org/10.1007/s11325-007-0135-9] [PMID: 18087741]
- [27] Bigham A, Bauchet M, Pinto D, *et al.* Identifying signatures of natural selection in Tibetan and Andean populations using dense genome scan data. *PLoS Genet* 2010; 6(9): e1001116. [http://dx.doi.org/10.1371/journal.pgen.1001116] [PMID: 20838600]
- [28] Siques P, López de Pablo AL, Brito J, *et al.* Nitric oxide and superoxide anion balance in rats exposed to chronic and long term intermittent hypoxia 2014. [http://dx.doi.org/10.1155/2014/610474]
- [29] Wilkins MR, Aldashev AA, Wharton J, *et al.* $\alpha 1$ -A680T variant in GUCY1A3 as a candidate conferring protection from pulmonary hypertension among Kyrgyz highlanders. *Circ Cardiovasc Genet* 2014; 7(6): 920-9. [http://dx.doi.org/10.1161/CIRCGENETICS.114.000763] [PMID: 25373139]
- [30] León-Velarde F, Mejía O. Gene expression in chronic high altitude diseases. *High Alt Med Biol* 2008; 9(2): 130-9. [http://dx.doi.org/10.1089/ham.2007.1077] [PMID: 18578644]
- [31] Morrell NW, Sarybaev AS, Alikhan A, Mirrakhimov MM, Aldashev AA. ACE genotype and risk of high altitude pulmonary hypertension in Kyrgyz highlanders. *Lancet* 1999; 353(9155): 814. [http://dx.doi.org/10.1016/S0140-6736(99)00206-8] [PMID: 10459973]
- [32] Aldashev AA, Sarybaev AS, Sydykov AS, *et al.* Characterization of high-altitude pulmonary hypertension in the Kyrgyz: association with angiotensin-converting enzyme genotype. *Am J Respir Crit Care Med* 2002; 166(10): 1396-402. [http://dx.doi.org/10.1164/rccm.200204-345OC] [PMID: 12406857]
- [33] León-Velarde F, Ramos MA, Hernández JA, *et al.* The role of menopause in the development of chronic mountain sickness. *Am J Physiol* 1997; 272(1 Pt 2): R90-4. [PMID: 9038995]
- [34] Netzer NC, Strohl KP. Sleep and breathing in recreational climbers at an altitude of 4200 and 6400 meters: observational study of sleep and patterning of respiration during sleep in a group of recreational climbers. *Sleep Breath* 1999; 3(3): 75-82. [http://dx.doi.org/10.1007/s11325-999-0075-7] [PMID: 11898112]
- [35] Ginosar Y, Malhotra A, Schwartz E. High altitude, continuous positive airway pressure, and obstructive sleep apnea: subjective observations and objective data. *High Alt Med Biol* 2013; 14(2): 186-9. [http://dx.doi.org/10.1089/ham.2012.1085] [PMID: 23795742]
- [36] Rosati JA, Yoneda KY, Yasmeen S, Wood S, Eldridge MW. Respiratory health and indoor air pollution at high elevation. *Arch Environ Occup Health* 2005; 60(2): 96-105. [http://dx.doi.org/10.3200/AEOH.60.2.96-105] [PMID: 16983862]

- [37] Vinnikov D, Blanc PD, Brimkulov N, Redding-Jones R. Five-year lung function observations and associations with a smoking ban among healthy miners at high altitude (4000 m). *J Occup Environ Med* 2013; 55(12): 1421-5. [<http://dx.doi.org/10.1097/JOM.0b013e3182a641e7>] [PMID: 24270292]
- [38] Rhodes CJ, Wharton J, Howard L, Gibbs JS, Vonk-Noordegraaf A, Wilkins MR. Iron deficiency in pulmonary arterial hypertension: a potential therapeutic target. *Eur Respir J* 2011; 38(6): 1453-60. [<http://dx.doi.org/10.1183/09031936.00037711>] [PMID: 21478213]
- [39] Xu XQ, Jing ZC. High-altitude pulmonary hypertension. *Eur Respir Rev* 2009; 18(111): 13-7. [<http://dx.doi.org/10.1183/09059180.00011104>] [PMID: 20956117]
- [40] Aldashev AA, Kojonazarov BK, Amatov TA, *et al.* Phosphodiesterase type 5 and high altitude pulmonary hypertension. *Thorax* 2005; 60(8): 683-7. [<http://dx.doi.org/10.1136/thx.2005.041954>] [PMID: 16061711]
- [41] Wagner GS, Strauss DG. *Marriott's practical electrocardiography*. 12th ed., Philadelphia: LWW 2013.
- [42] Audi SH, Dawson CA, Rickaby DA, Linehan JH. Localization of the sites of pulmonary vasomotion by use of arterial and venous occlusion. *J Appl Physiol* 1991; 70(5): 2126-36. [PMID: 1864795]
- [43] Negi PC, Marwaha R, Asotra S, *et al.* Prevalence of high altitude pulmonary hypertension among the natives of Spiti Valley--a high altitude region in Himachal Pradesh, India. *High Alt Med Biol* 2014; 15(4): 504-10. [<http://dx.doi.org/10.1089/ham.2013.1112>] [PMID: 25531464]
- [44] León-Velarde F, Maggiorini M, Reeves JT, *et al.* Consensus statement on chronic and subacute high altitude diseases. *High Alt Med Biol* 2005; 6(2): 147-57. [<http://dx.doi.org/10.1089/ham.2005.6.147>] [PMID: 16060849]
- [45] Mathai SC, Hassoun PM. Pulmonary arterial hypertension in connective tissue diseases. *Heart Fail Clin* 2012; 8(3): 413-25. [<http://dx.doi.org/10.1016/j.hfc.2012.04.001>] [PMID: 22748903]
- [46] Ahearn GS, Tapson VF, Rebeiz A, Greenfield JC Jr. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. *Chest* 2002; 122(2): 524-7. [<http://dx.doi.org/10.1378/chest.122.2.524>] [PMID: 12171826]
- [47] Fisher MR, Forfia PR, Chamera E, *et al.* Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009; 179(7): 615-21. [<http://dx.doi.org/10.1164/rccm.200811-1691OC>] [PMID: 19164700]
- [48] Kojonazarov BK, Imanov BZ, Amatov TA, *et al.* Noninvasive and invasive evaluation of pulmonary arterial pressure in highlanders. *Eur Respir J* 2007; 29(2): 352-6. [<http://dx.doi.org/10.1183/09031936.00137605>] [PMID: 17079253]
- [49] Sime F, Peñaloza D, Ruiz L. Bradycardia, increased cardiac output, and reversal of pulmonary hypertension in altitude natives living at sea level. *Br Heart J* 1971; 33(5): 647-57. [<http://dx.doi.org/10.1136/hrt.33.5.647>] [PMID: 5115010]
- [50] Fried R, Reid LM. Early recovery from hypoxic pulmonary hypertension: a structural and functional study. *J Appl Physiol* 1984; 57(4): 1247-53. [PMID: 6238924]
- [51] Richalet JP, Grataudour P, Robach P, *et al.* Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. *Am J Respir Crit Care Med* 2005; 171(3): 275-81. [<http://dx.doi.org/10.1164/rccm.200406-804OC>] [PMID: 15516532]
- [52] Xu Y, Liu Y, Liu J, Qian G. Meta-analysis of clinical efficacy of sildenafil, a phosphodiesterase type-5 inhibitor on high altitude hypoxia and its complications. *High Alt Med Biol* 2014; 15(1): 46-51. [<http://dx.doi.org/10.1089/ham.2013.1110>] [PMID: 24673534]
- [53] Seheult RD, Ruh K, Foster GP, Anholm JD. Prophylactic bosentan does not improve exercise capacity or lower pulmonary artery systolic pressure at high altitude. *Respir Physiol Neurobiol* 2009; 165(2-3): 123-30. [<http://dx.doi.org/10.1016/j.resp.2008.10.005>] [PMID: 18977464]
- [54] Kojonazarov B, Isakova J, Imanov B, *et al.* Bosentan reduces pulmonary artery pressure in high altitude residents. *High Alt Med Biol* 2012; 13(3): 217-23. [<http://dx.doi.org/10.1089/ham.2011.1107>] [PMID: 22994522]
- [55] Bärtsch P, Swenson ER. Acute high-altitude illnesses. *N Engl J Med* 2013; 369(17): 1666-7. [PMID: 24152275]
- [56] Richalet JP, Rivera M, Bouchet P, *et al.* Acetazolamide: a treatment for chronic mountain sickness. *Am J Respir Crit Care Med* 2005; 172(11): 1427-33. [<http://dx.doi.org/10.1164/rccm.200505-807OC>] [PMID: 16126936]
- [57] Smith TG, Talbot NP, Privat C, *et al.* Effects of iron supplementation and depletion on hypoxic pulmonary hypertension: two randomized controlled trials. *JAMA* 2009; 302(13): 1444-50.

[<http://dx.doi.org/10.1001/jama.2009.1404>] [PMID: 19809026]

- [58] Kojonazarov B, Myrzaakhmatova A, Sooronbaev T, Ishizaki T, Aldashev A. Effects of fasudil in patients with high-altitude pulmonary hypertension. *Eur Respir J* 2012; 39(2): 496-8.
[<http://dx.doi.org/10.1183/09031936.00095211>] [PMID: 22298615]

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