

High-Altitude Pulmonary Vascular Diseases

Maniraj Neupane, MBBS, PhD
Mountain Medicine Society of Nepal
Maharajgunj, Kathmandu, Nepal

Erik R. Swenson, MD
Department of Medicine
Section of Pulmonary and Critical Care
Medicine
VA Puget Sound Health Care System
University of Washington
Seattle, WA

More than 140 million people permanently reside in high-altitude regions of Asia, South America, North America, and Africa. Another 40 million people travel to these places annually for occupational and recreational reasons, and are thus exposed to the low ambient partial pressure of oxygen. This review will focus on the pulmonary circulatory responses to acute and chronic high-altitude hypoxia, and the various expressions of maladaptation and disease arising from acute pulmonary vasoconstriction and subsequent remodeling of the vasculature when the hypoxic exposure continues. These unique conditions include high-altitude pulmonary edema, high-altitude pulmonary hypertension, subacute mountain sickness, and chronic mountain sickness.

More than 140 million people permanently reside in high-altitude regions of Asia, South America, North America, and Africa. Another 40 million people travel to these places annually for occupational and recreational reasons, and are thus exposed to the low ambient partial pressure of oxygen. The critical human response to the hypoxic stress and challenge of high altitude includes the need to increase the capacity and efficiency of all steps in the cascade of oxygen flux from inhaled air to the respiring mitochondria. This entails increasing ventilation, cardiac output, and blood hemoglobin content, along with reducing the diffusive distances oxygen must traverse across the lung and tissue capillaries.¹ At the cellular level there are changes in capillary and mitochondrial density and in metabolic efficiency.² Beyond immediate increased peripheral chemoreceptor output and autonomic nervous system activation, hypoxia via the ubiquitous transcription factors, hypoxia-inducible factors (HIFs), also drive changes in the transcription of more than a thousand genes involved in enhancing tolerance to hypoxia.^{3,4} Most of these responses are physiologically useful, but not all, and in some cases even beneficial responses if too excessive can be maladaptive, such as with exaggerated polycythemia and elevation in pulmonary vascular resistance (PVR).

Short-term (minutes to days) acclimatization responses to hypobaric hypoxia differ from longer-term adaptations observed in individuals remaining at altitude for extended periods (months to years), and even more so in those populations that have resided at high altitude for many generations in the Himalayas, Andes, and Ethiopian plateau.

This review will focus on the pulmonary circulatory responses to acute and chronic high-altitude hypoxia, and the various expressions of maladaptation and disease arising from acute pulmonary vasoconstriction and subsequent remodeling of the vasculature when the hypoxic exposure continues. These unique conditions include high-altitude pulmonary edema (HAPE), high-altitude pulmonary hypertension (HAPH), subacute mountain sickness (SMS), and chronic mountain sickness (CMS).

PHYSIOLOGY OF THE PULMONARY CIRCULATION TO HYPOXIA

The pulmonary circulation responds to regional alveolar hypoxia (and hypercapnia) by redistributing blood flow to better ventilated lung areas⁵ to optimize ventilation-perfusion matching and improve gas exchange efficiency. Alveolar hypoxia is the main determinant of the local partial pressure of oxygen (PO_2) in the pulmonary vasculature, but systemic

arterial PO_2 via the bronchial (systemic) blood flow into the vaso-vasorum of the pulmonary vessels and mixed venous PO_2 also contribute. This mechanism, termed hypoxic pulmonary vasoconstriction (HPV), is mainly mediated by endothelial and smooth muscle cells of small pulmonary arteries and veins, and perhaps the capillary endothelium itself.⁶ Importantly, red cells, the autonomic nervous system, acid-base status, and numerous circulating and locally produced vasoactive substances further influence HPV in vivo.⁷ It occurs even with modest reductions in alveolar PO_2 such as appears with decreases in $F_{I}O_2$ to 0.15–0.18 or ascent above 5000 feet. Although activation of HPV in limited regions of the lung usually does not cause pulmonary artery pressure (PAP) elevation except in those with preexisting pulmonary hypertension (PH), when alveolar hypoxia is more global such as at high altitude or in extensive lung disease, diffuse HPV throughout the lung vasculature evokes an increase in PAP and PVR.^{7,8} PAP increases in a parabolic fashion with ever-increasing altitude such that a moderate increase in altitude over 8000 feet results in a greater increase in PAP (Figure 1).⁹ HPV and the rise in PAP demonstrate considerable (almost 5-fold) intraindividual and intraspecies variability,¹⁰ determined by genetic and structural differences.

With sustained exposure and even with chronic intermittent hypoxic exposures, the pulmonary vasculature responds by remodeling and strengthening itself against the high pressure.

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Correspondence: maniraj.neupane@gmail.com
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Remodeling is a complex process to higher pressure involving multiple cell types and occurs in the endothelium, muscle elements, and adventitia at all points in the circulation from the arteries to the veins.^{9,11} Higher pressure causes some degree of cellular proliferation and deposition of collagen and other extracellular matrix proteins. Chronic hypoxia can cause low-grade inflammation, which may also play a role in remodeling.¹¹ Again, in analogy to acute HPV, the extent of remodeling varies among individuals. It is unknown whether acute HPV is correlated with the extent of remodeling, but if remodeling is a response to elevated pressures it is reasonable to envision a causal linkage.

HIGH-ALTITUDE PULMONARY EDEMA

HAPE is the earliest of the pulmonary vascular diseases of high altitude. It was initially reported and described in 1960,^{12,13} as a potentially fatal condition that develops due to alveolar capillary leakage because of severe and regionally uneven HPV in susceptible individuals, but without any evidence of left ventricular dysfunction. It usually occurs after 1 to 4 days of ascending to high altitude in previously healthy individuals or in high-altitude residents upon return from extended lowland sojourns (termed re-entry HAPE). Although extremely rare, HAPE has been reported in people fully acclimated to high altitude.¹⁴ The rate of incidence of HAPE in lowlanders going to high altitude varies from 1% to 15% depending on altitude, rate of ascent, and individual susceptibility. Those with a prior history of HAPE have a very high (60%) likelihood of recurrence with the same ascent rate.¹⁵

HAPE is a noncardiogenic form of pulmonary edema characterized by dyspnea on exertion, which eventually progresses to dyspnea at rest with cough, chest tightness, and production of blood-tinged frothy sputum. Additional signs include tachycardia, cyanosis, severe arterial desaturation, and pulmonary rales. Chest radiographs show patchy peripheral infiltrates and nodular-like infiltrates on computed tomography (CT) imaging.

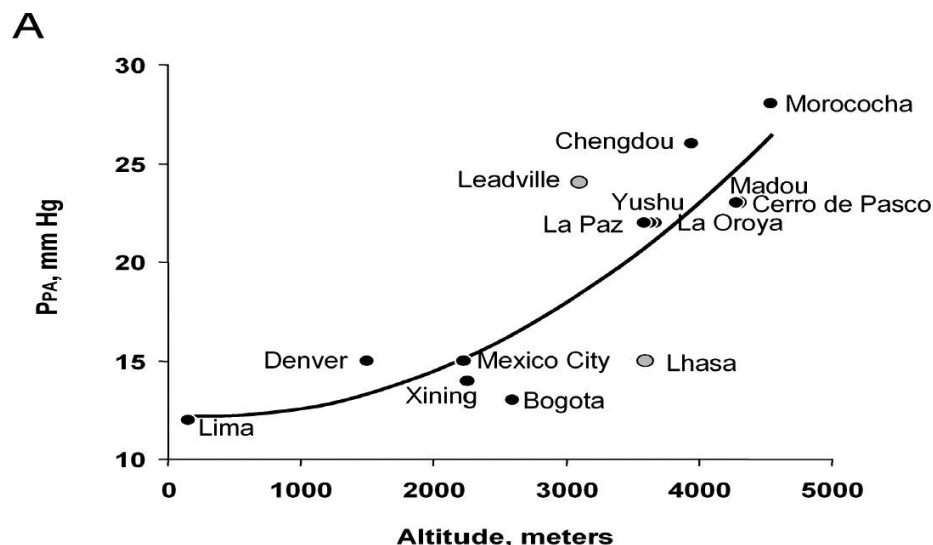


Figure 1: The relationship of pulmonary artery pressure and altitude is represented by a parabolic line such that a moderate increase in altitude above 3000 meters correlates with greater increase in pulmonary artery pressure, with exceptions in Leadville, Colorado (3100 meters) and Lhasa, Tibet (3600 meters). Reprinted with permission from Penalzo D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation*. 2007;115(9):1132-1146.

A cardinal feature of subjects with HAPE susceptibility is their very strong exaggerated HPV. Compared to their HAPE-resistant counterparts, HAPE-susceptible subjects develop an abnormally increased PAP when exposed to brief or prolonged hypoxia (Figure 2),^{16,17} but no elevation in left atrial pressure. Even during exercise in normoxic conditions, those susceptible to HAPE show a greater PAP rise, suggesting a constitutional hyper-reactivity of the pulmonary circulation to various stresses.^{17,18} In addition to strong HPV, nuclear imaging¹⁹ and magnetic resonance imaging (MRI) studies^{20,21} have demonstrated increased heterogeneity of regional pulmonary blood flow in HAPE-susceptible subjects during hypoxic breathing at rest, which would be predicted to be even more maldistributed with exercise and higher cardiac outputs. What causes this increase in regional heterogeneity of blood flow with hypoxia is unknown. One factor might be greater heterogeneity of regional ventilation that would cause more dispersion of regional alveolar PO_2 , but with functional lung MRI of regional ventilation, HAPE-susceptible subjects had surprisingly more, not less, uniform distribution of ventilation.²² Thus, it appears that the phenomenon of unevenness of HPV resides at the vascular

level. Despite the fact that HAPE is associated with exaggerated HPV, this response does not always lead to HAPE in all persons.^{23,24} Thus, HAPE susceptibility likely involves more than just a strong vasoconstrictor response to hypoxia.

As a consequence of nonhomogeneous local HPV, those regions with lesser HPV experience greater blood flow and with a higher pressure are the areas likely prone to leak. However, there has never been a direct test of this by measurements of greater lung density (increased lung water) corresponding to the areas of greater blood flow and lesser HPV. Unevenness in regional HPV may explain why CT imaging of HAPE often shows discrete nodular opacities rather than diffuse alveolar edema. Pulmonary artery catheterization studies done in mountaineers with HAPE at 4559 meters with analysis of the decay in downstream pressure after rapid inflation of the pulmonary artery catheter balloon demonstrate transmission of increased PAP to the pulmonary microvasculature,²⁵ similar to many earlier studies showing no evidence of left ventricular dysfunction by pulmonary artery wedge pressure measurement. The capillary pressure was estimated as high as 20-25 mm Hg, a threshold in a nonadapted circulation that can induce

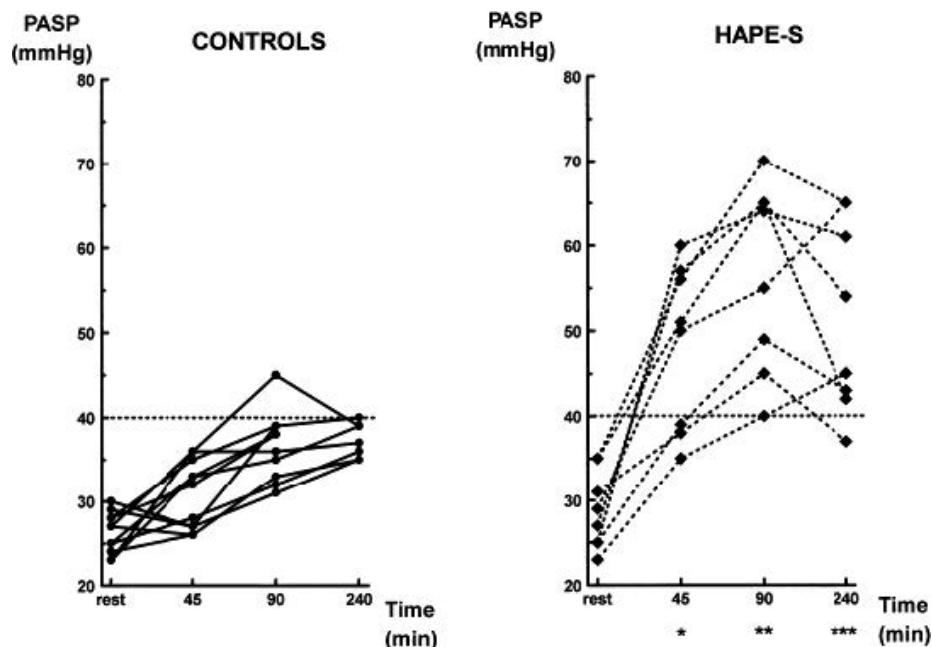


Figure 2: Pulmonary artery systolic pressure (PASP), estimated by Doppler echocardiography, increases abnormally in HAPE-susceptible (HAPE-S) subjects when exposed to hypoxia compared to their HAPE-resistant controls. Reprinted from Grunig E, Mereles D, Hildebrandt W, et al. Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. *J Am Coll Cardiol*. 2000;35(4):980-987, with permission from Elsevier.

traumatic breaks in the basement membranes of alveolar capillaries leading to hydrostatic leakage of protein-rich fluid and red blood cells into alveolar spaces as found in lavage studies described below.²⁶

Early bronchoalveolar lavage (BAL) studies done among climbers who developed HAPE on Mount McKinley found a protein-rich, sometimes bloody lavage fluid^{27,28} unlike that which would be expected with mild left ventricular dysfunction. Furthermore, a possible inflammatory process causing or exacerbating the edema was suspected, because in some victims there was increased number of alveolar macrophages and neutrophils, as well as complement activation and thromboxane generation noted in the lavage fluid.^{27,28} However, these lavage fluids were often obtained late in the course of illness, even as patients were improving. In a subsequent study performed within the first day of symptoms, subjects with profound arterial desaturation and new infiltrates on chest x-rays exhibited a protein-rich, mildly blood lavage fluid indicative of a hydrostatic pulmonary edema with altered alveolar-capillary permeability; however, there was no evidence of in-

flammation either by changes in resident alveolar immune cells or proinflammatory cytokines.²⁹

Being male,^{30,31} performing heavy exercise (such as mountaineering or skiing), and having or having had a recent viral respiratory infection³² increases the likelihood of developing HAPE. Depending on its size, a patent foramen ovale (PFO) may worsen the degree of arterial hypoxemia and increase the risk of HAPE.³³ The mechanism by which a PFO is linked to a greater incidence of HAPE is not fully understood. On the one hand, a diversion of blood past the lungs, all else being equal should lower the PAP, as is the strategy of atrial septostomy used as a last resort in severe PH. However, the greater hypoxemia generated by an intra-atrial right-to-left shunt could cause greater sympathetic activation, and with the resultant lower arterial oxygenation in the bronchial arterial blood and mixed venous blood lead to a lower PO_2 at the vasculature despite an equal alveolar PO_2 .

Other factors found to underlie HAPE susceptibility include a lower hypoxic ventilatory response (HVR) that sets a lower alveolar PO_2 and higher partial pressure of carbon dioxide

(PCO_2) for the same inspired PO_2 .³⁴ In addition, less hypoxic peripheral chemoreceptor sensitivity may also directly affect the pulmonary vasculature via efferent communication from the brain, since for the same alveolar and arterial PO_2 those with lower HVR have greater HPV.⁸ Subjects with lower HVR also have a much lower diuretic response to hypoxia,³⁵ which may lead to more pulmonary edema than in those that lose more salt and water in the initial several days at high altitude. Greater hypoxic sympathetic activation,³⁶ reduced vascular and nitric oxide (NO) generation and cyclic guanosine monophosphate (GMP) formation,^{29,37-39} and higher endothelin-1 release⁴⁰ have been demonstrated in HAPE-susceptible subjects. Although not as definitively established, polymorphisms of many genes involved in vasoactive mediator generation, inflammation, and the HIF pathway have been proposed,^{11,41-43} along with a reduced capacity to actively reabsorb sodium and water by the alveolar epithelium.^{44,45}

Prevention and Treatment of HAPE

A gradual ascent to high altitude such that the sleeping elevation gain is less than 500 meters per day with rest days incorporated after every 3 or 4 days has been recommended to prevent acute altitude illnesses including HAPE.⁴⁶ In those with a prior history of HAPE, prophylactic nifedipine is advised based on a randomized controlled trial in 21 HAPE-susceptible volunteers who ascended to 4559 meters.⁴⁷ Nifedipine, a calcium channel blocker known to inhibit HPV, reduces the incidence of HAPE by 90% by lowering systolic PAP. It has also been used for treatment of HAPE.⁴⁸ Other pulmonary vasodilators and HPV inhibitors, such as the phosphodiesterase type 5 (PDE5) inhibitor tadalafil, also reduce the occurrence of HAPE in susceptible individuals by blocking the degradation of cyclic GMP.⁴⁹ A somewhat surprising finding in the aforementioned study of tadalafil was that in a parallel arm of HAPE-susceptible subjects given dexamethasone, none developed HAPE—a 100% success rate. Dexamethasone was studied as an agent to enhance active

alveolar sodium and water reabsorption rather than a pulmonary vasodilator. Yet, dexamethasone lowered PAP equally as well as tadalafil at altitude when given prophylactically, but not in established HAPE, suggesting that its genomic actions and new gene transcription are critical. Counter to the expectation that dexamethasone would enhance alveolar fluid reabsorption, it did not affect any surrogate measures indicative of upregulation of epithelial sodium channels or sodium-potassium ATPase, 2 of the critical alveolar epithelial membrane ion transporters. By a mechanism unrelated to carbonic anhydrase inhibition, acetazolamide has been shown to be a potent inhibitor of HPV in humans and many other mammals,⁵⁰ to reduce HAPE in an animal model,⁵¹ and is used off-label by pediatricians in the Colorado Rockies to prevent reentry HAPE. In addition to its known ventilatory stimulation and diuretic effects, its inhibition of HPV makes it an attractive drug to use prophylactically, but formal studies need to be performed.

Descent to lower altitude should be advised for those with HAPE, or if descent is not possible then the patient should be treated with supplemental oxygen or placed inside a portable hyperbaric bag. Nifedipine or tadalafil should be administered as long as there is no hypotension. The patient should avoid exercise as this further increases PAP. Supplemental oxygen and bed rest alone with close observation may be all that is necessary in resort areas with medical facilities close at hand.⁵² Diuretics are not generally needed and likely dangerous in remote areas, since dehydration and volume depletion may be present in sick subjects.

HIGH-ALTITUDE PULMONARY HYPERTENSION

Chronic exposure to hypobaric hypoxia is responsible for the development of HAPH due to vascular structural remodeling.⁵³ It is classified as World Health Organization (WHO) Group 3.6 PH. It is diagnosed when the mean PAP is more than 30 mm Hg or when systolic PAP measured at the altitude of residence (at more than 2500 meters) is >50 mm Hg in those

without other chronic lung or cardiac conditions such as heart failure, chronic obstructive pulmonary disease, and interstitial lung disease.⁵⁴ While the prevalence of PFO in those living at high altitude (~32%) is no higher than in the general population, those with a PFO had slightly greater right ventricular enlargement and a much bigger increase in pulmonary artery systolic pressure with mild exercise.⁵⁵ Sleep apnea, both obstructive and central—the latter being the more common form at high altitude—may be important contributors to HAPH, since sleep-disordered breathing is far more common in those with HAPH than in those without it.⁵⁶

Although HAPH has been recognized for decades, its epidemiology is not well known. Considerable work in Kyrgyzstan, China, the Andes, and the Rockies would suggest that it is somewhat more prevalent in persons who were not born and raised at high altitude, but rather came to live at high altitude later in life. In a study of 741 Kyrgyz high-altitude residents, roughly 23% of males and 6% of females had electrocardiogram signs of cor pulmonale, and in a subset of these 75% had mean PAP of 31 mm Hg.⁵⁷ A later study by the same group in over 1400 inhabitants living above 2500 meters found a slightly lower prevalence of 4% to 6%.⁵⁸ In the Andes and in western China and Tibet, similar numbers have been reported.^{59,60}

The clinical presentation of HAPH is similar to any form of PH with exertional dyspnea as an early feature, but evolving as the disease progresses to general fatigue, anginal chest pain, syncopal episodes, and cor pulmonale in its late stages. Numerous genetic associations have been reported in small series of patients with HAPH, including gene polymorphisms in ACE (encoding angiotensin-converting enzyme),⁶¹ *EPAS1* (encoding HIF-2a),⁶² *GUCY1A3* (encoding soluble guanylate cyclase),⁶³ and *EGLN1* (encoding prolyl hydroxylase 2).⁶⁴ In contrast, the much lower PAP of native Tibetans is associated with different polymorphisms of *EPAS1* and *EGLN1* than those with HAPH described above.⁶⁵

Treatment of HAPH

Treatment of HAPH has been studied in small groups of subjects, with successful results reported with the Rho kinase inhibitor fasudil,⁶⁶ sildenafil,⁶⁷ and bosentan.⁶⁸ Although often not a practical solution for many reasons, HAPH resolves on moving to low altitude as the remodeled pulmonary circulation can undergo remodeling as has been shown in many animal models of hypoxic PH and inferred in humans.⁶⁹ Given the more profound hypoxemia occurring with sleep with even normal breathing and certainly in those with sleep apnea, nocturnal home oxygen during sleep could be useful, along with noninvasive positive airway pressure devices for sleep apnea, but this has not yet been tested.

SUBACUTE MOUNTAIN SICKNESS

The effects of hypoxia were described in cattle taken to summer mountain pastures in the Rocky Mountains in the early 1900s.⁷⁰ Many cattle developed severe congestive right heart failure with prominent edema in the jaws and chest muscles after spending several weeks at high altitude. This bovine form of SMS, also known as Brisket Disease, shows an autosomal dominant mode of heritability, but until recently the only predictive test to identify susceptible cattle was to measure PAP on arrival by catheterization. Genetic analysis had not been revealing in elucidating a hereditary basis until Newman and colleagues recently reported a gain-of-function mutation of *EPAS1* as a likely gene for HAPH in cattle.⁷¹ The importance of this finding is bolstered by the fact that *EPAS1* knockout mice have reduced HPV,⁷² and in humans a variant of *EPAS1* (a loss-of-function allele) in Tibetans appears to underlie the much lower PAP and hematocrit in this population.⁶⁵ Curiously, these cattle do not develop severe polycythemia as might be expected since *EPAS1* encodes the HIF (HIF-2a) that drives renal erythropoietin (*EPO*) gene transcription.⁷³

In humans, a similar pathology was reported among Indian soldiers posted to the Kashmir region in the India-Pakistan war of the 1960s.⁷⁴ These soldiers who were deployed at 5800 to 6700

meters developed slowly progressive congestive heart failure with generalized edema and severe shortness of breath after spending about 3 months at these extremely high altitudes. They developed minimal polycythemia, right ventricular enlargement, and pericardial effusion, but by auscultation, no evident pulmonary edema. Catheterization studies done at 300 meters within 72 hours of return from high altitude revealed mild PH that was not responsive to oxygen inhalation.⁷⁴ Their heart failure resolved spontaneously within 2 weeks of transfer to lower altitude. All hemodynamic parameters returned to normal by 12 to 16 weeks.⁷⁴ Only about 10% to 20% of soldiers stationed at high altitude developed SMS, and it is not known what factors increase the susceptibility to this condition. Whether, like in cattle, a variant of *EPAS1* in humans is responsible has not been investigated since the incidence of SMS has been so markedly diminished by better acclimatization strategies and shorter postings to extreme altitudes.

Although PAP was never measured in these soldiers while at high altitude, the residual PH documented on their return to near sea level is suggestive of an underlying structural remodeling that takes about 12 to 16 weeks to resolve.⁷⁵ In the absence of lung biopsies, there are no histological data to compare with findings in an infantile form of SMS wherein pulmonary arterioles show extreme muscularization.⁷⁶ Like the adult manifestation of SMS, infants of Han Chinese who migrated to the Qinghai-Tibetan plateau⁷⁷ develop severe PH as a result of extreme muscularization of pulmonary arterioles, only minimally responsive to oxygen inhalation.⁷⁶ They progressed to right heart failure and had to descend to lower altitude to recover and survive.^{75,77}

CHRONIC MOUNTAIN SICKNESS

Carlos Monge described a unique condition: CMS among Peruvian native highlanders in 1925.⁷⁸ CMS is a clinical syndrome occurring in lifelong high-altitude natives at >2500 meters, which is characterized by severe erythrocytosis (hemoglobin [Hb] values of ≥ 19 g/dL

for women and ≥ 21 g/dL for men) and severe hypoxemia⁵⁴ in the absence of secondary conditions that themselves cause hypoxemia. Patients with CMS have inappropriately elevated or normal EPO concentrations in relation to their polycythemia.⁷⁹ CMS prevalence varies depending on ethnic groups. In the Andes, the prevalence is highest and increases with age and altitude of residence. It is much more common in men than women, with a prevalence of 15.4% in men between 30 and 39 years and up to a third of men in their sixth decade of life at 4340 meters in the Andes.⁸⁰ In the Tibetan plateau, however, its prevalence is only around 1% to 2%. It has a similar low prevalence in North America.⁸¹ The reasons for the much greater prevalence of CMS in the Andes may be genetic, but other factors such as occult cobalt toxicity have been found.⁸²

Clinical features in CMS include an array of neurological symptoms like fatigue, headache, confusion, sleep disturbances, dizziness, and alterations of memory and concentration. Other symptoms including breathlessness, palpitations, localized cyanosis, anorexia, bone and joint pain are also present.⁵⁴ Clinical signs include ruddy color, hypoxemia and excessive erythrocytosis, and hematocrit of 70% to 90% compared to 55% in healthy controls. Due to polycythemic hyperviscosity, those with CMS are prone to arterial and venous thrombosis, stroke, and myocardial infarction in early adulthood. Sleep-disordered breathing and greater nocturnal oxygen desaturation is more common in those with CMS,^{83,84} and the associated sleep disruption may contribute to the mental symptoms of CMS and the higher oxidative stress.^{83,85}

Although it is reported that cor pulmonale develops in CMS due to PH, it is uncertain how often right heart failure truly complicates CMS. PH is relatively moderate in CMS and does not appear to limit exercise capacity in middle-age patients compared to age-matched controls.^{86,87} Mice that constitutively overexpress EPO demonstrate a marked upregulation of endothelial NO synthase and vascular NO production, which likely helps to moderate both systemic and pulmonary hypertension.⁸⁸ Whether

this is the case in CMS has not been determined, but might be expected as it is known that EPO upregulates endothelial vascular and red cell NO synthase expression and activity.^{89,90} The degree to which elevated pressures and reduced cardiac output in CMS are due to polycythemia, and its associated hyperviscosity has been studied with isovolemic hemodilution.⁹¹ In this study of 8 subjects with CMS and Hb greater than 19 g/dL, normovolemic phlebotomy lowering the Hb content from 21.5 to 18.2 g/dL had a reduction of PVR from 3.9 to 3.1 Wood units. The fall in mean PAP was less (27 to 25 mm Hg) because the cardiac output rose considerably from 5.5 to 6.9 L/min. Interestingly, ventilation-perfusion mismatching was reduced and ventilation rose by 1.5 L/min (15%) with hemodilution. Relative hypoventilation in those with CMS compared to healthy altitude controls is thought to drive the polycythemia,⁹² as it leads to greater hypoxemia and thus higher Hb concentrations. However, the hemodilution data suggest that the development of polycythemia may cause hypoventilation rather than being the initial problem.

With the advent of genomic technologies, molecular mechanisms of the genetic susceptibility of CMS are being explored. *SENPI* (sentrin-specific protease 1), an erythropoietic regulator, has been identified by Cole et al⁹³ and Zhou et al⁹⁴ as playing a role in those developing CMS. On the other hand, the presence of specific single nucleotide polymorphisms in *EPAS1* and *EGLN1* in Tibetan highlanders who have a lower hemoglobin concentration can be linked to a mechanism that offers protection against CMS. To date there have been no findings of differences in *EPO* or the *EPO* receptor genes in CMS.⁹²

Treatment of CMS

The treatment of CMS is relocation to low altitude as the symptoms disappear after moving to low altitude. Isovolemic phlebotomy safely reduces hematocrit, improves ventilation, improves arterial saturation, and decreases PAP.⁹¹ Ventilatory stimulants such as acetazolamide 250 mg/day increase ventilation during sleep and wakefulness

and increase oxygen saturation with a drop in erythropoietin, hematocrit, and a reduction of symptoms.^{95,96} Two recent randomized controlled trials showed that treatment for 3 months reduced PVR, increased cardiac output, and maintained oxygen delivery despite a 6% to 10% fall in hematocrit. Medroxyprogesterone (20 to 60 mg/day for 10 weeks) increases ventilation and normalizes PaO₂ and P_AO₂.⁹⁷ ACE inhibitors⁹⁸ and theophylline may be effective by reducing renal EPO secretion.

CONCLUSION

The ambient inspired hypoxia of high altitude elevates PAP and PVR in all individuals, but only some develop disease related to these changes. A summary of the conditions discussed in this review is provided in Table 1.

The first of these conditions is HAPE, which occurs in lowlanders in the first few days after ascending to altitudes above 2500 meters. It is caused by an excessive degree of HPV and owing to a likely heterogeneous regional intensity of HPV, where those areas

of the lung with the least increase in HPV are subjected to high blood flow and pressure that exceed the structural load-bearing capacity of the alveolar capillary barrier. The edema is a non-cardiac, high-protein, noninflammatory, mild hemorrhagic capillary leak that can be life-threatening, but if descent and/or treatment are successfully initiated, full recovery will occur without residual damage or persisting PH. Prevention depends on slower ascent rates and prophylactic nifedipine, PDE5 inhibitors, and possibly acetazolamide, all

Table 1. Summary of High-Altitude Pulmonary Vascular Diseases, Clinical Features, and Management

High-Altitude Pulmonary Vascular Diseases	Epidemiology And Exposure	Symptoms And Signs	Prevention Modalities	Treatment Modalities
High-altitude pulmonary edema	Develops in 1%-15% of lowlanders going to high altitude within 1-4 days of ascent with or without preceding symptoms of acute mountain sickness or high-altitude cerebral edema.	Dyspnea with exertion evolving to breathlessness at rest with associated arterial desaturation and cyanosis, dry cough progressing to production of pink frothy sputum, pulmonary rales on auscultation, and patchy infiltrates on chest x-ray.	Gradual ascent avoiding exertion and elevations gain limited to 500 meters per day. For those with prior history of HAPE, prophylactic nifedipine is recommended. Phosphodiesterase inhibitors and acetazolamide may also have role for prophylaxis.	Observation with supplemental oxygen and rest suffices for mild condition, while descent to lower altitude remains the mainstay of treatment. Exertion should be avoided during descent. Portable hyperbaric chamber is useful if descent is not feasible. Nifedipine or phosphodiesterase inhibitors are used for moderate to severe cases; however, dual therapy should be avoided due to risk of hypotension.
High-altitude pulmonary hypertension	Prevalent in those who were not born and raised at high altitude, but who later migrate to these regions.	Exertional dyspnea evolving to general fatigue, anginal chest pain, and syncopal episodes.		Resolves with moving to low altitude while medical therapy can be tried with fasudil, sildenafil, and bosentan.
Subacute mountain sickness	Reported among cattle, infants, and adults after weeks to months of high altitude exposure.	Dyspnea, cyanosis, and signs of right-sided heart failure with peripheral edema, hepatomegaly, and ascites.	Gradual ascent allowing acclimatization with shortened duration of stay at high altitude.	Descent to lower altitude reverses the changes in pulmonary vasculature.
Chronic mountain sickness	Affects lifelong high-altitude residents or natives at >2500 meters with considerable variability among different high-altitude population. Prevalence ranges from 1% in Tibetans to as high as 33% among elderly Andeans.	Headache, dizziness, breathlessness, sleep disturbances, fatigue, alterations of memory and concentration with underlying excessive erythrocytosis, severe hypoxemia, hyperviscosity, and pulmonary hypertension.	Periodic travel to lower altitude offsets rise in hematocrit.	Relocation to lower altitude or sea level is the definitive means, while phlebotomy with or without isovolemic hemodilution reduces hematocrit and pulmonary artery pressure. Acetazolamide, theophylline, medroxyprogesterone, and angiotensin-converting enzyme inhibitors may be effective.

of which inhibit HPV and lower PAP. Treatment includes descent, oxygen, nifedipine, and PDE5 inhibitors. Patients with PH and underlying lung disease should largely avoid altitude exposure unless breathing supplemental oxygen.

The second form of high-altitude pulmonary disease is HAPH, which develops in some individuals after chronic residence at high altitude. This form of PH (WHO Group 3.6) can often be treated by moving back to low altitude, because the greater vasoconstriction and remodeling will reverse. If return to lower altitude is not possible, then standard oral medications such as PDE5 inhibitors, endothelin receptor blockers, and prostacyclin analogs may be used. Because of greater sleep-related desaturation at altitude, use of nocturnal oxygen may also be advised. In a rarer form of HAPH called subacute mountain sickness, some individuals at very high altitudes may develop right heart failure after several months of exposure, such as occurs in cattle with Brisket Disease.

A final form of PH at high altitude is CMS. This condition has as its defining hallmark an excessive increase in red cell production and elevated hematocrit (>70%) that leads to blood hyperviscosity, PH, cor pulmonale, and thrombotic complications. Treatment includes acetazolamide, theophylline, ACE inhibitors, phlebotomy, and descent.

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