High-Altitude Illness and Muscle Physiology

Wayne M. Weil, M.D., Philip J. Glassner, M.D., and Joseph A. Bosco, III, M.D.

Abstract

High-altitude illness is a growing concern in sports medicine that affects persons shortly after they have climbed to a new high-altitude level to which their body is not acclimatized. With the increasing popularity of extreme sports, such as high-altitude mountaineering, skiing, and snowboarding, the incidence of complications arising from sports activities at high altitudes is increasing. High-altitude pulmonary edema and high-altitude cerebral edema are potentially fatal conditions. The study of high-altitude muscle physiology has broad ramifications in creating training programs for elite endurance athletes. A thorough understanding of the pathophysiology, presentation, treatment, and prevention of high-altitude illness is necessary for the treatment of these patients.

igh-altitude illness (HAI) is a spectrum of cerebral and pulmonary syndromes that develop in nonacclimatized persons shortly after ascent to a new, higher altitude. Specifically, HAI includes acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) (Table 1). While much attention has been given to these illnesses of late, the first written description of HAI was made by Too Kin, a

Wayne M. Weil, M.D., was a Chief Resident in the NYU Hospital for Joint Diseases Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, New York, New York. Philip J. Glassner, M.D., is currently a Resident in the NYU Hospital for Joint Diseases Department of Orthopaedic Surgery. Joseph A. Bosco, III, M.D., is Assistant Professor of Orthopaedic Surgery, NYU School of Medicine, and Attending in the Sports Medicine Service, NYU Hospital for Joint Diseases Department of Orthopaedic Surgery, New York, New York.

Correspondence: Joseph A. Bosco, M.D., Suite 8U, New York University Medical Center, 530 First Avenue, New York, New York 10016.

Chinese government official during, approximately, 37 to 32 BC. The presentation he described was that a "man's face turns pale, his head aches, and he begins to vomit."1,2 Our difficulties in adaptation to high altitudes may have something to do with our species evolution. Recent phylogenetic reconstructions suggest that the genus *Homo* evolved not at sea level, but rather, at elevations of 1000 to 2000 m in the African highlands. This may have ultimately led to evolutionary adaptations, causing some to hypothesize that altitude tolerance for humans is, in fact, ancestral.3 Humans have a degree of inherent ability to adapt to high altitudes, but there are populations, and some persons, who are able to do so more comfortably then others. The inhabitants of the Andean altiplano, in the Andes Mountains of South America, have been living and thriving at altitudes of over 3000 m for more than 10,000 years.4

In contemporary times, humans have desired to climb ever higher. Maurice Herzog and Louis Lachenal, in 1950, became the first climbers to reach an 8000 m peak.⁵ Since that time, many thousands of adventurers have traveled to Pakistan, Nepal, Tibet, and China to climb one of the 14 peaks that rise above 8000 meters, with Mt. Everest being the highest point on Earth at 8848 m.⁶

With the increasing popularity of extreme sports (high-altitude mountain climbing, alpine skiing, and snowboarding) and the ease and availability of travel in current times, millions of people are exposed, annually, to the danger of HAI. In Pheriche, Nepal (altitude of 4343 m), 43% of trekkers experienced symptoms of AMS.⁷ Further, in studies performed on a more general tourist population in the Colorado ski resorts, Honigman described the incidence of AMS to be 22% at 1850 m to 2750 m, while Dean showed 42% to have symptoms at an altitude of 3000 m.^{8,9} Due to these high percentages of illness at moderately high altitudes and the fact that many of the highest mountains also have poor medical facilities, physicians and travelers must understand

Table 1 High-Altitude Illness (HAI)

Туре	Altitude	Pathophysiology	Symptoms	Treatment	Prevention
Acute Mountain Sickness (AMS)	≥ 2500 m	Hypoxia Increased cerebral blood flow Increased intracranial pressure	Headache GI symptoms	Hydration Halt ascent Acetazolamide	Acclimatization at altitude Gradual ascent Avoid alcohol Hydrate NSAIDs
High-altitude Pulmonary Edema (HAPE)	48 hrs at ≥ 2500 m	Pulmonary hypertension Hypoxia: vasoconstriction of blood vessels vasodilation of systemic vessels	Dyspnea Dry cough Fever Lethargy	Halt ascent Oxygen Nifedipine	[same as for AMS] Nifedipine
High-altitude Cerebral Edema (HACE)	2 to 4 days at ≥ 5500 m	Hypoxia Capillary leakage Cerebral edema	Headache Altered mental status Ataxia	Immediate descent Oxygen Dexamethasone	[Same as for AMS] Dexamethasone

the risks, signs, symptoms, and treatment of HAI.

Risk Factors

There are multiple risk factors for HAI, with the most reliable predictor being a prior history from previous climbs. ¹⁰ Other common risk factors include the rate of ascent, the altitude reached, sleeping altitude, residence at an altitude less than 900 m, individual physiology, preexisting cardiopulmonary conditions, age, and gender. It has been shown that persons under 50 years of age are less susceptible to AMS, ¹¹ and that females are less prone to high-altitude pulmonary edema, but equally prone to AMS. ⁸ A recent study has suggested an association of obesity and HAI. After 24 hours in a controlled, simulated experiment, seven obese males (78%) compared with four nonobese males (40%) had AMS scores indicative of HAI. ¹²

High-Altitude Illness

Lack of oxygen is the primary cause of HAI. Barometric pressure declines exponentially with altitude, becoming so low that heights greater than 8000 m are inhospitable for sustaining human life. On Mount Everest this is known as the "death zone," an appelation that reflects the high potential for a cascade of catastrophic events associated with HAI. Oxygen comprises 21% of air at any altitude; therefore, as altitude increases available oxygen decreases. The limits of oxygen exchange at higher altitudes are due to the following: 1) lower driving pressure for oxygen diffusion from air to blood; 2) lower affinity of hemoglobin for oxygen on the steep part of the oxygen dissociation curve; and 3) decreased time for equilibration of oxygen as red blood cells traverse the pulmonary capillaries.

Physiologically, much of the above is due to oxygen's interaction with hemoglobin. Hemoglobin is made up of four subunits, two alpha and two beta polypeptide chains. When a molecule of oxygen binds to hemoglobin, it causes a conformational change, increasing the affinity of the remaining binding sites for oxygen. This is known as cooperative binding, and is the reason for the sigmoid shape of the oxygen.

gen dissociation curve. This also explains why hemoglobin is most attracted to oxygen when three of the four subunits are bound to oxygen.

At a wide range of physiologic oxygen partial pressures (PO_2 60 mm to 100 mmHg) hemoglobin oxygen saturation is greater than 90%. However, at a PO_2 of less than 60 mmHg, the oxygen content of hemoglobin drops precipitously, with further small decreases in PO_2 . This has obvious implications at high altitude, since the oxygen tension at the peak of Mt. Everest is approximately 43 mmHg.¹³ Although, at this altitude, hemoglobin is still greater than 50% saturated, since the P_{50} is about 26.6 mmHg in a healthy person.

There are several factors that cause a shift in the P_{50} , which include changes in carbon dioxide, temperature, [H⁺], and 2,3-diphosphoglycerate (2,3 DPG). Increases in these factors cause a right shift of the P_{50} on the O_2 dissociation curve, allowing unloading of O_2 from hemoglobin to the tissues. To the contrary, a decrease in any of the above factors causes a leftward shift of the curve, increasing the affinity of hemoglobin for oxygen.^{7,13}

The ventilatory system responds to decreases in oxygen tension by maintaining constant levels of carbon dioxide. Carbon dioxide is the main stimulus to ventilation, but at altitudes greater than 3000 m (inspired oxygen pressure 13.3 kPa), hypoxia increases ventilation. This response is mediated by the carotid body and is proportional to an individual's inherent hypoxic ventilatory response (HVR).¹⁴ The HVR increases the respiratory rate, leading to a respiratory alkalosis and an increased arterial oxygen saturation. For example, at a normal sea level, P₅₀ of 26 mmHg, the expected arterial oxygen saturation on the peak of Mt. Everest (PO₂) 43 mmHg) would be 55%, which is not compatible with human life. When the HVR takes effect, it causes a respiratory alkalosis, or a decreased [H+] and an increased blood pH. These events, in turn, cause a leftward shift of the P₅₀ to 20 mmHg, thus, increasing the arterial oxygen saturation to 78%. 13 This allows climbers to survive for a short time without supplemental oxygen. However, a brisk HVR does not necessarily correlate with an increased ability to tolerate high altitude. As the HVR increases, so does one's respiratory rate, and with that comes an increase in labored breathing. This increased work associated with breathing causes the respiratory muscles themselves to consume more oxygen, possibly burning more oxygen than is taken up by the increase in breathing rate.¹⁴

A further adaptation is made by the muscles. After prolonged exposure to high altitudes, one develops a loss of muscle volume, which at first appears detrimental. On closer examination, this may, in fact, be beneficial, because as muscle volume diminishes, the capillary density remains the same. This setting provides for an improvement in oxygen diffusion to the remaining muscle, possibly improving one's functional ability.15 Therefore, there is a delicate balance between shifting the P₅₀ to the right (unloading oxygen to the tissues) and to the left (increasing the arterial oxygen saturation) in an attempt to maximize one's ability to function at high altitudes. Interestingly, even elite climbers cannot maintain this balance successfully for long periods and they must adapt to the decreased oxygen partial pressures at high altitudes. Thus, even the most well trained athletes have been found to be susceptible to HAI.¹⁶

Pathophysiology

Acute mountain sickness is defined as the presence of a headache in a person who has recently arrived at an altitude of 2500 m and must include one or more of the following: GI symptoms (anorexia, nausea, vomiting), insomnia, dizziness, or fatigue. ¹⁷ Headache is the most common symptom (48%) followed by GI symptoms (24%). ¹⁸ The headaches are throbbing, either bitemporal or occipital and often worse at night or on awakening. ¹⁹ These symptoms usually begin, approximately, 4 to 12 hours after an ascent to an elevation greater than 2500 m. ^{19,20}

AMS may progress to HACE, which is characterized by a more global cerebellar dysfunction. Persons often present with a worsening headache, ataxic gait, severe lassitude, altered mental status, drowsiness, stupor, and coma. Severe cases may include hallucinations, paresthesias, vertigo, diplopia, cranial nerve palsies, hemiparesis, hemiplegia, and seizures. On fundoscopic exam, one may notice papilledema and retinal hemorrhages although the hemorrhages are usually asymptomatic. 19,20

The progression to HACE usually occurs 2 to 4 days after ascent to an altitude greater than 2500 meters but is more common above 5500 m (2% to 3% of mountain climbers), and rare without concurrent HAPE.²⁰ If HACE is left untreated, it can rapidly lead to death from brain herniation.

Hypoxia is the initiating event in both HACE and HAPE and elicits neurohumoral and hemodynamic responses that result in the over perfusion of microvascular beds, elevated hydrostatic capillary pressure, capillary leakage, and consequent brain edema. The exact cause of these events is unknown. A leading hypothesis holds that a leak occurs in the blood-brain barrier, secondary to hypoxia that allows

fluid to accumulate, thus increasing the intracranial pressure. Possible mediators are free radicals, bradykinin, histamine, nitric oxide, and vascular endothelial growth factor. 18,21

Individual susceptibility to AMS/HACE may be related to one's ability to accept an increased volume of cerebral spinal fluid. This idea is supported by the fact that the elderly are less susceptible to AMS. As humans age, the size of the brain decreases, but the cranial vault remains the same size, creating more space for an accumulation of fluid and delaying the onset of symptoms. 18 Due to the severe consequences of HACE, treatment should be instituted as soon as suspicion arises. Further, even with proper treatment (see below), the effects may be permanent. A study by the American Medical Research Expedition to Everest found that a year after return to sea level many climbers had abnormal cognitive functioning as well as a decreased ability to perform fast, repetitive movements.7 Other considerations when evaluating someone for AMS/HACE include an alcohol hangover, influenza, migraine, dehydration, substance abuse, and hypothermia.²²

HAPE Symptoms and Pathophysiology

High-altitude pulmonary edema occurs because hypoxia is a vasodilator of the systemic circulation and a vasoconstrictor of the pulmonary circulation. This leads to pulmonary hypertension. The mechanism is multifactorial with increased sympathetic activity, endothelial dysfunction, hypoxemia from a poor ventilatory response to hypoxia, and elevated capillary pressure. The elevated microvascular pressure leads to stress failure of pulmonary capillaries, causing extravasation of plasma and cells into the alveoli. A study by Swenson and colleagues suggested that the elevated pressure may alter the structure of the alveolar membrane by relaxing tight junctions and forming transcellular, vesicular channels. Both of these changes support the idea of a noninflammatory, unidirectional leak found in HAPE.²³ The high protein leakage that is created decreases the ability of oxygen to flow from the alveoli to the capillaries, which can lead to a death similar to drowning.22

HAPE usually presents the second night after a rapid ascent to an altitude greater than 2500 m and rarely after four days at a given altitude. It is possible for HAPE to occur at moderate altitudes of 1400 m to 2400 m, as shown in a recent study conducted in the French Alps. In this study, 52 patients vacationing at a moderate altitude presented with hypoxemia and radiographic signs of pulmonary edema. Further, 96% had dyspnea and 77% had moist rales, demonstrating that the occurrence of HAPE at moderate altitudes may be greater than expected.²⁴

The most common presentation of HAPE is symptoms of AMS along with dyspnea on exertion, dry cough, decreased exercise performance, fatigue, and fever. The condition may progress to dyspnea at rest, cyanosis, tachycardia, and neurologic symptoms.²⁵ Late in the illness, the cough may become productive with pink bloody sputum, and respiratory

distress may develop.²⁶ If distress becomes severe, death may occur; HAPE is the most common cause of death from HAI.²⁰

On physical examination, rales are often heard in the right axilla and may become bilateral later in the illness. An arterial blood gas will show severe hypoxemia, with a partial pressure of arterial oxygen of 30 mm to 40 mmHg and a respiratory alkalosis. An EKG will show sinus tachycardia and signs of right heart strain, such as right axis deviation, right bundle branch block, and P-wave abnormalities. Radiographic signs are usually present, including full pulmonary arteries and patches of fluffy infiltrates with areas of clearing in the right lower and middle lobes in mild cases and both lungs in severe cases. Cardiomegaly is not seen, as HAPE is not a cardiogenic process. ^{20,26} This presentation is similar, however, to other conditions which should be considered, such as asthma, bronchitis, myocardial infarction, pneumonia, and pulmonary embolus. ²⁶

HAI Treatment

Treatment of HAI follows three axioms: 1) further ascent should be halted until symptoms have resolved, 2) patients who do not respond to medical treatment should descend to a lower altitude, and 3) at the first sign of HACE, patients should descend to a lower altitude. Patients are descent and supplementary oxygen. A descent of 500 m to 1000 m may be sufficient with mild symptoms of cerebral edema, but with more severe symptoms, further descent and additional measures should be taken. Patient on of these measures is a simulated descent in a portable hyperbaric chamber. A chamber pressure of 2 psi is equivalent to a decrease in altitude of 2000 m. A commonly used portable hyperbaric chamber, known as the Gamow bag, can be used for simulated descents of up to 600 meters when a climber cannot be moved.

Oxygen therapy should be administered at the highest flow possible until oxygen saturation can be monitored.²² Increasing alveolar and arterial oxygenation is the highest priority, since breathing supplemental oxygen reduces pulmonary artery pressure by 30% to 50%.^{27,28} It should be administered by mask or nasal cannula at an initial rate of 2 to 4 liters/min, then decreased to 1 to 2 liters/min, or titrated to an SaO₂ greater than 90%. This measure is lifesaving for HAPE and improves headaches in AMS within minutes.²⁶

Several other medications are used for the treatment of HAI, with acetazolamide, dexamethasone, and nifedipine being used most often.²⁵ Acetazolamide is used primarily for the treatment of AMS and is given at 125 mg to 250 mg po BID until symptoms resolve.

This agent functions as a carbonic anhydrase inhibitor, causing a metabolic acidosis and speeding natural acclimatization. The outcome includes bicarbonate diuresis and respiratory stimulation, an increase in PaO2, a reduction in the formation of CSF, and a promotion of ion transport across the blood-brain barrier. Side effects include distal

paresthesias, polyuria, and a change in the taste of carbonated beverages. 19,26

Dexamethasone may be used for the treatment of AMS or HACE, but is ineffective in the treatment of HAPE. For AMS, a dose of 4 mg is administered every 6 to 12 hours by oral, IV, or IM route. For treatment of HACE, 8 mg is given initially, then 4 mg every 6 hours by oral, IM, or IV administration. The exact mechanism of action is unknown, but this agent may reduce brain edema, which would create relief in HACE. It is thought that for the treatment of AMS dexamethasone functions by reducing nausea and improving mood. Common side effects include rebound sickness and hyperglycemia. ^{19,22,26}

Nifedipine is used for the treatment of HAPE, and has no effect on AMS or HACE. Initially, it is given at a dose of 10 mg orally, then 20 mg to 30 mg extended release formulation every 12 hours. Nifedipine is a calcium channel blocker, reducing pulmonary artery pressure and pulmonary vascular resistance. A major possible complication is that of lowering systemic arterial pressure, which may impair cerebral perfusion in a concomitant HACE. For this reason, nifedipine is often avoided.^{7,26}

A novel treatment for HAPE is the use of inhaled nitric oxide (NO). It has been shown in people with HAPE who inhale NO, blood flow in the lungs is redistributed from areas of edema to nonedematous areas, improving ventilation and perfusion. Surprisingly, in climbers who were are resistant to HAPE, NO actually decreased arterial oxygenation, even though it relieved pulmonary vasoconstriction.²⁹

Prevention

The most effective method of preventing HAI is allowing time for acclimatization, followed by a gradual measured ascent. As a general rule, one should ascend gradually once above an altitude of 2500 m. Sleeping altitude should not be increased by more than 600 m in 24 hours, and an extra day should be added for acclimatization for every increase in sleeping altitude of 600 to 1200 m.^{25,26} As an example of the effectiveness of this approach, Purkayastha and associates showed that a gradual ascent to an altitude of 3500 m over four days reduced the incidence and severity of AMS by 41%, compared to ascending to the same altitude in one hour.³⁰ Most climbers follow the "climb high, sleep low" approach, in which one climbs higher during the day and then partially descends to their eventual sleeping altitude. 25,26 Other recommendations include minimal exercise for 24 hours after abrupt elevation to 2500 meters or above, minimizing alcohol usage, maintaining hydration, and ingesting a high carbohydrate diet.¹⁹

Due to the body's natural response to hypoxia, physical training at high altitudes is used to improve athletic performance at high altitude. This is largely due to induced secondary polycythemia increasing one's work capacity at altitude. Both nonathletes and elite endurance athletes have maximal reticulocytosis after about 8 to 10 days at moderate altitude.

Training periods of three weeks at moderate altitudes result in individual increases of hemoglobin concentration of about 1% to 4%.³¹

Multiple medications have been used for the prevention of HAI and its associated symptoms and include aspirin, acetazolamide, and dexamethasone. Aspirin has been used for headache prophylaxis at a dose of 325 mg orally every 4 hours for three doses; this regimen reduces headache incidence from 50% to 7%. For prophylaxis against AMS, acetazolamide given at 125 mg to 250 mg po BID, 24 hours before ascent, and for the first two days at high altitude has been found to be effective. Dexamethasone at a dose of 2 mg orally every 6 hours or 4 mg orally every 12 hours has also been effective at preventing AMS. ²⁶

Less rigorously tested preventative measures include nifedipine, red wine, salmeterol, and EGb 761 (i.e., ginkgo biloba). Nifedipine has been used with mixed results for the prevention of HAPE at a dose of 20 mg to 30 mg extended release formula every 12 hours. ²⁶ It has been observed that mountaineers often consume red wine in order to "feel better," seemingly paradoxical, because alcohol should be detrimental at high altitudes by suppressing respiration. In a recent article, two mechanism have been postulated. First, some of the compounds of red wine suppress endothelin-1 gene expression (endothelin-1 acts to increase pulmonary vascular tone), and second, red wine has antioxidative properties. The combination of these two effects may be beneficial. ³³

Sartori and coworkers recently reported on the use of salmeterol for the prevention of HAPE. The day before an ascent to 4559 m, participants received either 125 mg of salmeterol (about three times the normal asthma dosage) or placebo every 12 hours via a metered-dose inhaler with a spacer. The climbers were than observed for two days and nights, during which time the incidence of pulmonary edema was significantly less in the salmeterol group than in the placebo group $(74\% \text{ vs. } 33\%; p = .02).^{34}$

Ginkgo biloba has been evaluated in various studies and has shown promising results for the prevention of AMS. One of the most promising includes the study of 44 trekkers in Nepal at altitudes of up to 5400 m. In this investigation, none of the participants who were given ginkgo biloba (160 mg BID) developed AMS, compared with 41% of the placebo treated group (p < 0.001).³⁵ The exact mechanism creating this effect is unknown at this time. The effectiveness of ginko biloba and other treatments are indeed promising, but because of established efficacy in preventing AMS, acetazolamide or dexamethasone should remain first-line agents for prevention of HAI, until further studies are conducted.

Conclusions

HAI is becoming a common problem of both mountaineers and casual tourists. The increasing popularity of travel to and sports participation in high-altitude environments has caused an increased incidence in HAI. In Colorado alone, approximately 20% of tourists at ski resorts experience AMS.¹⁹ With our current understanding of the causes and treatment of HAI, many cases should be preventable. Education is the key to successfully limiting the number of people who fall prey to HAI. If people traveling to high altitudes take the proper precautions and remember to "climb high, but sleep low," the devastating effects of severe HAI can be prevented.

References

- Tso E. High altitude illness. Emerg Med Clin North Am. 1992 May;10(2):231-47.
- Gilbert DL. The first documented report of mountain sickness: The China or headache mountain story. Respir Physiol. 1983 Jun;52(3):315-26.
- Dudley R. Limits to human locomotor performance: Phylogenetic origins and comparative perspectives. J Exp Biol. 2001 Sep;204(Pt 18):3235-40.
- Rupert JL, Hochachka PW. Genetic approaches to understanding human adaptation to altitude in the Andes. J Exp Biol. 2001 Sep;204(Pt 18):3151-60.
- Huey RB, Eguskitza X. Limits to human performance: Elevated risks on high mountains. J Exp Biol. 2001 Sep;204(Pt 18):3115-3119.
- West JB. Barometric pressures on Mt. Everest: New data and physiological significance. J Appl Physiol. 1999 Mar;86(3):1062-6.
- Peacock AJ. ABC of oxygen: Oxygen at high altitude. BMJ. 1998 Oct 17;317(7165):1063-6.
- Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. Ann Intern Med. 1993 Apr 15;118(8):587-92.
- Dean AG, Yip R, Hoffmann RE. High incidence of mild acute mountain sickness in conference attendees at 10,000 foot altitude. J Wilderness Med. 1990;1:86-92.
- Bartsch P, Grunig E, Hohenhaus E, Dehnert C. Assessment of high altitude tolerance in healthy individuals. High Alt Med Biol. 2001 Summer;2(2):287-96.
- Roach RC, Houston CS, Honigman B, et al. How well do older persons tolerate moderate altitude? West J Med. 1995 Jan;162(1):32-6.
- Ri-Li Ge, Chase PJ, Witkowski S, et al. Obesity: Associations with acute mountain sickness. Ann of Intern Med. 2003 Aug 19;139(4):253-7.
- Hsai CC. Mechanisms of disease: Respiratory function of hemoglobin. N Engl J Med. 1998 Jan 22;338(4):239-47.
- Schoene RB. Limits of human lung function at high altitude.
 J Exp Biol. 2001 Sep;204(Pt 18):3121-7.
- Hoppeler H, Vogt M. Muscle tissue adaptations to hypoxia. J Exp Biol. 2001 Sep;204(Pt 18):3133-9.
- Westerterp KR. Limits to sustainable human metabolic rate. J Exp Biol. 2001 Sep;204(Pt 18):3183-7.
- The Lake Louise Consensus on the definition and quantification of altitude illness. *In:* Sutton JR, Coates G, Houston CS (eds). *Hypoxia and Mountain Medicine*. Burlington, Vermont: Queen City Press, 1992, pp. 327-330.
- Roach RC, Hackett PH. Frontiers of hypoxia research: Acute mountain sickness. J Exp Biol. 2001 Sept;204(Pt 18):3161-70.

- Kirsch DB, Jozefowicz RF. Neurologic complications of respiratory disease. Neurol Clin. 2002 Feb;20(1):247-64.
- Kuo DC, Jerrard DA. Environmental insults: Smoke inhalation, submersion, diving, and high altitude. Emerg Med Clin North Am. 2003 May;21(2):475-97.
- Schoch HJ, Fischer S, Marti HH. Hypoxia-induced vascular endothelial growth factor expression causes vascular leakage in the brain. Brain. 2002 Nov;125(Pt 11):2549-57.
- 22. Yarnell PR, Heit J, Hackett PH. High-altitude cerebral edema (HACE): The Denver/Front Range experience. Semin Neurol. 2000;20(2):209-17.
- Swenson ER, Maggiorini M, Mongovin S, et al. Pathogenesis of high-altitude pulmonary edema. JAMA. 2002 May 1;287(17):2228-35.
- Gabry AL, Ledoux X, Mozziconacci M, Martin C. High-altitude pulmonary edema at moderate altitude (< 2,400 m; 7,870 feet): A series of 52 patients. Chest. 2003 Jan;123(1):49-53.
- 25. Townes DA. Wilderness medicine. Prim Care. 2002 Dec;29(4):1027-48.
- Hackett JR, Roach RC. High-altitude illness. N Engl J Med. 2001 Jul 12;345(2):107-14.
- Oelz O, Maggiorini M, Ritter M, et al. Nifedipine for high altitude pulmonary edema. Lancet. 1989 Nov 25;2(8674):1241-4.
- 28. Hackett PH, Roach RC, Hartig GS, et al. The effect of

- vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: A comparison. Int J Sports Med. 1992 Oct;13(Suppl 1):S68-71.
- Scherrer U, Vollenweider L, Delabays A, et al. Inhaled nitric oxide for high-altitude pulmonary edema. N Engl J Med. 1996 Mar 7;334(10):624-9.
- Purkayastha SS, Ray US, Arora BS, et al. Acclimatization at high altitude in gradual and acute induction. J Appl Physiol. 1995 Aug; 79(2):487-92.
- Berglund B. High-altitude training. Aspects of haematological adaptation. Sports Med. 1992 Nov;14(5):289-303.
- Burtscher M, Likar R, Nachbauer W, Philadelphy M. Aspirin for prophylaxis against headache at high altitudes: Randomised, double blind, placebo controlled trial. BMJ. 1998 Apr 4;316(7137):1057-8.
- Schäfer A, Bauersachs J. High-altitude pulmonary edema: Potential protection by red wine. Nutr Metab Cardiovasc Dis. 2002 Oct;12(5):306-10.
- Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med. 2002 May 23;346(21):1631-6.
- 35. Roncin JP, Schwartz F, et al. EGb 761 in control of acute mountain sickness and vascular reactivity to cold exposure. Aviat Space Environ Med. 1996 May;67(5):445-52.