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High Altitude Illness
Pathogenesis and treatment

Abstract

As more people travel to high altitudes for economic or recreational purposes, altitude medicine has become increasingly important. High altitude illness is a term used to describe a number of acute syndromes that may occur in unacclimatized individuals at high altitude including *acute mountain sickness* (AMS), *high altitude pulmonary edema* (HAPE) and *high altitude cerebral edema* (HACE). Major risk factors for developing high altitude illness include the rate of ascent, the altitude reached, the altitude at which the person sleeps, and individual susceptibility. In both the brain and the lungs, hypoxia elicits neurohumoral and hemodynamic responses that result in overperfusion of microvascular beds, elevated hydrostatic capillary pressure, capillary leakage, and consequent edema. Evidence is accumulating that cerebral swelling trough vasodilation or cerebral edema, or both, is responsible for the symptoms and signs of AMS and HACE. HAPE results from the conjunction of a defect in pulmonary endothelial (exaggerated altitude-induced pulmonary vasoconstriction) and epithelial (impaired transepithelial sodium and water transport) function. Inflammation reported in HAPE is most likely a nonspecific response to stress-induced failure of capillaries and alveolar flooding, rather than part of the initial pathophysiological process.
The main principles of high-altitude illnesses treatment are to stop further ascent, to descend if symptoms do not improve over 24 hours or deteriorate, and to descend urgently if signs of HAPE or HACE occur. Acetazolamide and dexamethasone are the most effective drugs in the treatment and prevention of AMS and HACE while oxygen, if available, is the most effective treatment of HAPE. Oxygen not only reduces pulmonary artery pressure but it also reverses the extreme arterial hypoxemia of HAPE, thus protecting the brain and other organs. Nifedipine, a potent pulmonary vasodilator, is the drug of choice for the treatment of HAPE while nifedipine, salmeterol and possibly phosphodiesterase-5 inhibitors such as sildenafil represent an effective preventive drug therapy in susceptible individuals.

Key words:
high altitude illness, acute mountain sickness, high altitude pulmonary edema, high altitude cerebral edema

Zusammenfassung

Die Bedeutung der Höhenmedizin hat stark zugenommen, da immer mehr Menschen in ihrer Freizeit oder für ihren Beruf in sehr hoch gelegene Gebiete reisen. Die Höhenerkrankungen umfassen mehrere akute Syndrome, die bei unakklimatisierten Individuen in grosser Höhe auftreten können, wie die *akute Bergkrankheit* (AMS), das *Höhenlungenödem* (HAPE) und das *Höhenhirnödem* (HACE). Risikofaktoren für das Auftreten dieser Höhenerkrankungen sind die Aufstiegsgeschwindigkeit, die absolut erreichte Höhe, die Höhe, auf der geschlafen wird, sowie die individuelle Empfindlichkeit. Im Gehirn und in der Lunge führt die Hypoxie zu neurohumoralen und hämodynamischen Reaktionen, die eine Hyperperfusion und einen erhöhten hydrostatischen Druck und ein Leck der Kapillaren verursachen. Bei ungenügenden Kompensationsmechanismen entsteht schlussendlich ein Ödem. Die Evidenz nimmt zu, dass eine erhöhte Permeabilität (vasogenes Ödem) der Blut-Hirn-Schranke und eine osmotische Schwellung der Hirnzellen (zytotoxisches Ödem) für die Zeichen und Symptome sowohl von AMS und von HACE verantwortlich sind. Voraussetzung für das Auftreten eines Höhenlungenödems (HAPE) ist die Kombination von vorbestehenden Defekten des pulmonalen Endothels (überschiessende hypoxie-induzierte Vasokonstriktion) und des alveolären Epithels (gestörter trans-epithelialer Natrium- und Wassertransport). Die beim Höhenlungenödem beobachtete Entzündung ist eher eine unspezifische Reaktion auf das kapilläre Leck und die alveoläre Flüssigkeitsansammlung als Teil des eigentlichen pathophysiologischen Vorganges.
Die Therapie der akuten Höhenkrankheiten beinhaltet zur Hauptsache ein Stopp des weiteren Aufstiegs und – wenn sich die Symptome nicht innert 24 Stunden bessern bzw. sofort bei Zeichen eines HACE oder HAPE – den unverzüglichen Abstieg. Acetazolamide und Dexamethason sind die wirksamsten Medikamente zur Therapie und Prävention von AMS und HACE. Sauerstoff ist die wirksamste Therapie des HAPE; er reduziert nicht nur den pulmonal-arteriellen Druck, sondern verbessert auch die massive arterielle Hypoxämie und schützt somit das Gehirn und andere Organe. Nifedipine, ein potenter Vasodilatator, ist das Medikament der ersten Wahl zur Therapie des HAPE. Zur Prävention können ebenfalls Salmeterol und voraussichtlich auch Phosphodiesterase-5-Inhibitoren wie Sildenafil gegeben werden.

Schlüsselwörter:
Höhenkrankheit, akute Bergkrankheit, Höhenlungenödem, Höhenhirnödem

Schweizerische Zeitschrift für «Sportmedizin und Sporttraumatologie» 53 (2), 88–92, 2005

Introduction

Ambient pressure falls as altitude increases [1]. As a result, the higher one climbs, the lower the barometric pressure and the partial pressure of ambient oxygen. On the summit of Mount Everest, where the barometric pressure is 253 mmHg, the ambient oxygen tension is 53 mmHg and arterial oxygen saturation is around 30% [1].

As more people travel to high altitudes for economic or recreational purposes, altitude medicine has become increasingly important. Physiologically, high altitude begins at altitudes around 2500 m, where arterial oxygen saturation falls to values lower than 90%. High altitude illness is usually mild and self limiting but, rarely it may progress to more severe forms, which can be life threatening. High altitude illness is a term used to describe a number of acute syndromes that may occur in unacclimatized individuals at high altitude including *acute mountain sickness* (AMS), *high altitude pulmonary edema* (HAPE) and *high altitude cerebral edema* (HACE). The pathogenesis, clinical recogni-

tion, and management of high altitude disease, particularly HAPE is reviewed here. Chronic forms of mountain sickness, such as Monge disease, seen in South American Indians of the Andes are not discussed [2].

Risk factors

Risk factors for developing high altitude illness include the rate of ascent, the altitude reached, the altitude at which the person sleeps, and individual susceptibility [3] *(Table 1)*. Interactions between genes and environment most likely explain this individual susceptibility (or relative resistance) to high altitude illness, especially HAPE. Support for this comes from studies that noted a significant association between HAPE and specific polymorphisms of the endothelial nitric oxide synthase gene, the angiotensin-converting enzyme (ACE) gene, and the human leukocyte antigens (HLA)-DR6 and DQ4 [4]. Pregnancy and common preexisting illnesses such as coronary artery disease, hypertension, diabetes, chronic obstructive pulmonary disease do not affect the susceptibility to high altitude illness [3]. Physical fitness is not protective and exertion at altitude increases the risk.

Predicting high altitude illnesses, particularly HAPE, with tests performed at sea level remains illusory. Hypoxic challenge tests assessing hypoxic ventilatory and pulmonary vascular responses are still not sufficiently sensitive and specific enough to reliably predict who will develop HAPE. For now, only a history of HAPE is useful in identifying such subjects.

Acute mountain sickness and high altitude cerebral edema

AMS is the most common form of the altitude diseases. Its incidence varies according to geographic location and altitude [3, 5].

- Prior history of high-altitude illness
- Rapid ascent
- Actual altitude reached, sleeping altitude
- Intensity of physical activity
- Residence at an altitude < 1000 m
- Age < 50 years

Main additional risk factors specific for HAPE:

- Individual predisposition
- Young age
- Male gender
- Airway infection
- Cold
- Re-entry phenomena
- Primary or secondary pulmonary artery hypertension

Table 1: Risk factors for high altitude illness.

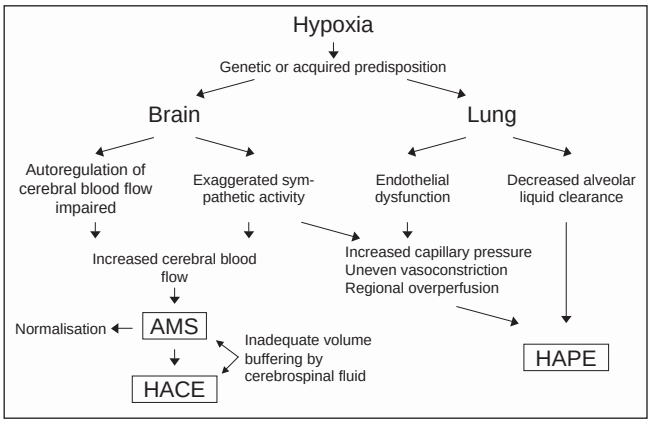

Figure 1: Pathogenetic mechanisms of high altitude illnesses. See text for details.

Definition and diagnosis

AMS is a syndrome of non-specific symptoms. Most common symptoms of AMS are headache, poor sleep, anorexia, fatigue, dizziness, lightheadedness, nausea, and vomiting [3, 5] *(Table 2)*. They occur usually 6–12 hours after arrival at a new altitude but may occur sooner. Usually the symptoms resolve spontaneously over 2–3 days. In contrast to HACE, there are no objective physical signs on clinical examination.

HACE is a clinical diagnosis, defined as the onset of ataxia, altered consciousness, or both in someone with AMS or HAPE [3] *(Table 2)*. Seizures are uncommon. Patients with HACE may present either slowly with confusion and loss of coordination, or rapidly with coma. Associated signs of HACE may include papilledema and retinal hemorrhage which is, however, a common incidental finding. Patients usually present with globally diminished neurologic function rather than focal deficits. Subjects should be evaluated for confusion and loss of finger-to-nose or heel-to-toe coordination.

Pathophysiology

The pathogenesis of AMS remains unknown. In both the brain and the lungs, hypoxia elicits neurohumoral and hemodynamic responses that result in overperfusion of microvascular beds, elevated hydrostatic capillary pressure, capillary leakage, and consequent edema *(Fig. 1)*. Evidence is accumulating that cerebral swelling trough vasodilation or cerebral edema, or both, is responsible for the symptoms and signs of AMS and HACE. The «tight fit» hypothesis postulates that individuals who anatomically can accommodate less cerebrospinal fluid within the cranio-spinal vault may be at higher risk for developing acute mountain sickness as mild brain swelling develops at altitude [3].

Treatment and prevention

The main principles of treating AMS are to stop further ascent, to descend if symptoms do not improve over 24 hours or deteriorate, and to descend urgently if signs of HAPE or HACE occur.

AMS	HACE	HAPE
• Headache • Anorexia, nausea, vomiting • Sleep disorders • Asthenia	• Severe headache • Ataxia • Altered consciousness • Coma	• Severe lassitude • Tachypnea, dyspnea at rest • Dry cough, haemoptysis • Subfebrile temperature (≈ 38°C) • Rales

Table 2: Clinical manifestations of AMS, HACE and HAPE.

AMS	HACE	HAPE
Prevention		
• Acclimatization, avoid intensive activity during first 2-5 days. • Slow and progressive ascent to altitude. See also Table 4. • Sufficient fluid intake and carbohydrate rich diet.		
• **Acetazolamide** [250mg / 8-12 hours, day -1 to 3] • **Dexamethasone** May be an option in some circumstances (see HACE).	• **Acetazolamide** (see AMS) • **Dexamethasone** [2-4mg / 6 hours, day 0 to 3; reduce dosage progressively over 5 days]	• **Nifedipine slow release** [Slow release form (20-30mg) 20-30mg / 8 hours, day -1 to 4] • **Salmeterol** inhalation [125µg / 12 hours, day -1 to 4]
Treatment		
• Stop climbing • Descent by 500m to 1000m • **Acetazolamide** [250mg / 8 hours] • **Dexamethasone** [4mg / 6 hours] • Symptomatic treatment with **analgesics** and **antiemetics**	• Immediate evacuation to low altitude • Oxygen • Hyperbaric chamber • **Dexamethasone** [8mg / 6 hours, po, iv or im]. Add: • **Acetazolamide** [250mg / 8 hours]	• Immediate evacuation to low altitude • Oxygen • Hyperbaric chamber • **Nifedipine slow release** (20-30mg / 8 hours) • **Dexamethasone** [8mg / 6 hours, if neurologic deterioration]

Table 3: Prevention and treatment of AMS, HACE and HAPE.

Table 3 resumes the treatment and prevention strategies of AMS and HACE and *Table 4* gives recommendations for maximum rates of ascent.

Acetazolamide is a carbonic anhydrase inhibitor that causes bicarbonate diuresis and, consequently, respiratory stimulation. The latter increases partial pressure of oxygen. Acetazolamide probably also reduces the formation of cerebrospinal fluid. It is recommended for treatment of AMS and, preventively, for people who are susceptible to acute mountain sickness and when ascent rates are unavoidably greater than those recommended. If preventively used, treatment should be started one day before ascent and continued until adequate acclimatization is judged to have occurred. Side effects, which include paresthesia, alteration of the taste of carbonated beverages and mild diuresis, are common but usually well tolerated. Acetazolamide is a sulphonamide, and allergic reactions can occur [3, 5].

Dexamethasone (2–4 mg every 6 hours) may be considered for the treatment of severe AMS and is unequivocally the drug of choice in the treatment of HACE [3, 5]. Used preventively, it reduces the incidence and severity of AMS. Prophylaxis may be started a few hours before ascent. However, dexamethasone should not be the first choice for the prophylaxis of AMS because of its side effects. These include mood changes, hyperglycemia, dyspepsia and rebound effect on withdrawal. It may, however, be useful in people who have to ascend rapidly or who are predisposed to severe AMS and are intolerant of or allergic to acetazolamide. Prophylactic treatment with dexamethasone should be as short as possible.

- Above 3000 meters increase your sleeping altitude by only 300-600 meters per day.
- Above 3000 meters take a rest day for every 1000 meters of elevation gained.
- Different people will acclimatise at different rates.
- If possible, don't fly or drive directly to high altitude.
- If you do go directly to high altitude by car or plane, do not overexert yourself or move higher for the first 24 hours.
- "Climb high and sleep low".
- If symptoms are not improving, delay further ascent.
- If symptoms deteriorate, descent as soon as possible.

Table 4: Acclimatization and rates of ascent.

High altitude pulmonary edema

High altitude pulmonary edema is a form of noncardiogenic pulmonary edema that is potentially fatal [3, 5, 6]. The syndrome generally occurs among otherwise healthy unacclimatized individuals who rapidly ascend to altitudes above 2500 m. Individuals who have experienced HAPE in the past are at high risk for recurrence: they are «HAPE-susceptible» or «HAPE-prone» [6, 7]. HAPE accounts for a majority of deaths due to high altitude disease. Risk factors for HAPE are resumed in *Table 1.*

Definition and diagnosis

High altitude pulmonary edema may appear insidiously over the course of several hours but may also present explosively and can, in contrast to HACE, occur without preceding AMS. Symptoms of HAPE consist of cough, breathlessness out of proportion to work, breathlessness that does not respond to rest, and production of frothy, often rusty, sputum. Physical findings at this time may include tachycardia, rapid breathing, cyanosis, elevated jugular venous pressure, and diffuse crackles on auscultation of the lungs *(Table 2)*. Unrecognized or untreated HAPE can rapidly worsen and end fatally. Patients with HAPE tend to have lower oxygen saturations than unaffected people at the same altitude, but the degree of desaturation by itself is not a reliable sign of HAPE [5]. When available, chest x-ray reveals diffuse patchy interstitial changes typical of non-cardiogenic pulmonary edema.

Pathophysiology

Several recent studies allowed a better comprehension of the pathogenesis of HAPE.

The usual pulmonary hypertension on ascent to high altitude is excessive in those with HAPE, as a result of exaggerated hypoxic pulmonary vasoconstriction [3, 5, 6, 8, 9]. Among the mechanisms contributing to this abnormal increase in pulmonary vascular resistance, sympathetic hyper-reactivity [10] and pulmonary endothelial dysfunction, characterized by an imbalance between vasoconstrictors [11] and dilators [12], play a major pathogenetic role. Maggiorini and co-workers reported that pressure was also

elevated at the level of the pulmonary capillaries with 19 mmHg being the apparent threshold for clinical HAPE [9]. Hultgren proposed that, as a consequence of uneven hypoxic pulmonary vasoconstriction, the microcirculation is protected in vasoconstricted areas but that less constricted areas are overperfused, causing elevated capillary pressure and capillary leakage [13] *(Fig. 1)*. The reduction of pulmonary artery pressure by the administration of potent vasodilators such as nifedipine [14] or nitric oxide (NO) [12] in HAPE-susceptible subjects supports the aforementioned concepts.

In the respiratory system, NO is not only produced by the pulmonary vascular endothelium, but also by the respiratory epithelium, and there is evidence that the latter also regulates pulmonary artery pressure [15]. Respiratory epithelial, but not pulmonary endothelial, NO synthesis can be assessed by measuring NO in the exhaled air. In HAPE-prone subjects, exhaled NO at high altitude is lower than in control subjects, and there exists an inverse relationship between pulmonary-artery pressure and exhaled NO at high altitude [15, 16].

On the basis of recent research, the inflammation reported in HAPE is most likely a nonspecific response to stress-induced failure of capillaries and alveolar flooding, rather than part of the initial pathophysiological process [17].

Thus, one could believe that exaggerated pulmonary hypertension is a sufficient condition to develop HAPE. We found, however, that at high altitude, young healthy subjects who had suffered from transient perinatal hypoxic pulmonary hypertension had exaggerated pulmonary hypertension as compared to controls that had not suffered from that perinatal complication [18]. Despite pulmonary vasoconstriction of similar magnitude to that observed in HAPE-prone subjects, none of these young adults developed HAPE [19]. These data challenge previous concepts and indicate that exaggerated hypoxic pulmonary vasoconstriction, while consistently associated with HAPE, is not sufficient to trigger pulmonary edema and suggest that additional mechanisms play a role.

Pulmonary edema results from an imbalance between the forces that drive fluid into the airspace (related to exaggerated pulmonary hypertension in the case of HAPE) and those responsible for its removal. Transepithelial sodium transport plays an important part in the removal of excess intraalveolar fluid [20]. Mice with an infraclinical defect of the transepithelial sodium transport have an augmented susceptibility to hypoxia-induced lung edema [6, 20]. Most interestingly, transepithelial sodium and water transport is impaired in HAPE-prone subjects, a defect which may be further aggravated by high-altitude exposure [20, 21]. In order to evaluate the clinical impact of this defect as well as its possible eligibility as a therapeutic target, we tested whether the prophylactic inhalation of the beta-adrenergic agonist salmeterol at a dose shown to stimulate the clearance of alveolar fluid decreases the incidence of pulmonary edema during exposure to high altitude in subjects who are prone to HAPE [20]. Compared to the placebo group, salmeterol decreased the incidence of HAPE in the treated group by approximately 60% [20], a prophylactic effect comparable with that of nifedipine [22].

Beyond the pathogenesis of HAPE, transepithelial sodium transport may be a potentially important mechanism in the pathophysiology of other disease states associated with augmented alveolar flooding and hypoxia, such as heart failure and the acute respiratory distress syndrome, both burdened with a high morbidity and mortality. Consequently, beta-adrenergic stimulation of the clearance of alveolar fluid may represent a novel therapeutic strategy to prevent such potentially fatal outcomes.

Taken together, the data are consistent with the hypothesis that HAPE results from the conjunction of a defect in pulmonary endothelial (exaggerated altitude-induced pulmonary vasoconstriction) and epithelial (impaired transepithelial sodium and water transport) function *(Fig. 2)*.

Treatment and prevention

Descent is the mainstay of treatment. Descent of even a few hundred meters may be beneficial. Supplemental oxygen should be given if available. Oxygen is the most effective treatment because it not only reduces pulmonary artery pressure but it also reverses the extreme arterial hypoxemia of HAPE, thus protecting the brain and other organs. Nifedipine is effective in preventing and treating high altitude pulmonary edema in susceptible individuals [14, 22] *(Table 3)*. A portable hyperbaric chamber pressurized by means of a manual pump (and thereby simulating descent) is an alternative treatment, particularly if descent has to be delayed.

Preventive strategies are resumed in *Table 3*. Preventive drug therapy with nifedipine [22] or salmeterol [20] can be considered in subjects known to be susceptible to HAPE. Preliminary data suggest that the phosphodiesterase-5 inhibitor sildenafil may improve exercise tolerance at high altitude by attenuating the effect of alveolar hypoxia on pulmonary artery pressure [23, 24].

Additional resources

Additional resources dealing with high altitude illnesses and particular conditions such as pregnancy, older and younger age, preexisting medical conditions, and the approach of an unconscious patient can be found elsewhere [5, 25]. *Table 5* gives some interesting internet links for doctors and potential patients.

- The International Society for Mountain Medicine (www.ismmed.org)
- The International Mountaineering and Climbing Federation (www.uiaa.ch)
- The Swiss Alpine Club (www.sac.ch)
- The German Alpine Association (www.alpenverein.de)
- The Wilderness Medical Society (www.wms.org)
- Bibliography of High Altitude Medicine and Physiology with over 8000 references (http://annie.cv.nrao.edu/habibqbe.htm)

Sites for travellers:

- www.high-altitude-medicine.com
- www.ciwec-clinic.com
- www.cdc.gov/travel/diseases/altitude.htm
- http://m-ww.de/reisemedizin/hoehenkrankheit.html

Table 5: Additional internet resources.

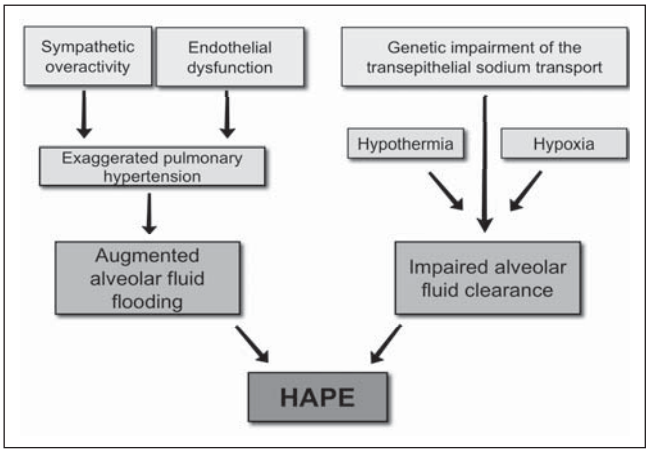

Figure 2: High altitude pulmonary edema (HAPE) results from the conjunction of a defect in pulmonary endothelial (exaggerated altitude-induced pulmonary vasoconstriction) and epithelial (impaired transepithelial sodium and water transport) function. See text for details.

Acknowledgements

We thank our colleagues and friends from Lausanne, particularly Urs Scherrer and Claudio Sartori, who were stimulating us for many years.

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References

1 *West JB:* The physiologic basis of high-altitude diseases. *Ann Intern Med* 141: 789–800, 2004.
2 *Monge CC, Whittembury J:* Chronic mountain sickness. *Johns Hopkins Med J* 139: 87–89, 1976.
3 *Hackett PH, Roach RC:* High-altitude illness. *N Engl J Med* 345: 107–114, 2001.
4 *Mortimer H, Patel S, Peacock AJ:* The genetic basis of high-altitude pulmonary oedema. *Pharmacol Ther* 101: 183–192, 2004.
5 *Barry PW, Pollard AJ:* Altitude illness. *Bmj* 326: 915–919, 2003.
6 *Scherrer U, Sartori C, Lepori M, Allemann Y, Duplain H, Trueb L, Nicod P:* High-altitude pulmonary edema: from exaggerated pulmonary hypertension to a defect in transepithelial sodium transport. *Adv Exp Med Biol* 474: 93–107, 1999.
7 *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* 297: 1269–1272, 1977.
8 *Allemann Y, Sartori C, Lepori M, Pierre S, Melot C, Naeije R, Scherrer U, Maggiorini M:* Echocardiographic and invasive measurements of pulmonary artery pressure correlate closely at high altitude. *Am J Physiol Heart Circ Physiol* 279: H2013–H2016, 2000.
9 *Maggiorini M, Melot C, Pierre S, Pfeiffer F, Greve I, Sartori C, Lepori M, Hauser M, Scherrer U, Naeije R:* High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation* 103: 2078–2083, 2001.
10 *Duplain H, Vollenweider L, Delabays A, Nicod P, Bartsch P, Scherrer U:* Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. *Circulation* 99: 1713–1718, 1999.
11 *Sartori C, Vollenweider L, Loffler BM, Delabays A, Nicod P, Bartsch P, Scherrer U:* Exaggerated endothelin release in high-altitude pulmonary edema. *Circulation* 99: 2665–2668, 1999.
12 *Scherrer U, Vollenweider L, Delabays A, Savcic M, Eichenberger U, Kleger GR, Fikrle A, Ballmer PE, Nicod P, Bartsch P:* Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 334: 624–629, 1996.
13 *Hultgren HN:* High-altitude pulmonary edema: current concepts. *Annu Rev Med* 47: 267–284, 1996.
14 *Oelz O, Maggiorini M, Ritter M, Waber U, Jenni R, Vock P, Bartsch P:* Nifedipine for high altitude pulmonary oedema. *Lancet* 2: 1241–1244, 1989.
15 *Scherrer U, Turini P, Thalmann S, Hutter D, Salinas Salmon C, Stuber T, Shaw S, Jayet P, Sartori-Cucchia C, Villena M, Allemann Y, Sartori C:* Pulmonary hypertension in high-altitude dwellers: novel mechanisms, unsuspected predisposing factors. *Adv Exp Med Biol*, In press, 2005.
16 *Duplain H, Sartori C, Lepori M, Egli M, Allemann Y, Nicod P, Scherrer U:* Exhaled nitric oxide in high-altitude pulmonary edema: role in the regulation of pulmonary vascular tone and evidence for a role against inflammation. *Am J Respir Crit Care Med* 162: 221–224, 2000.
17 *Swenson ER, Maggiorini M, Mongovin S, Gibbs JS, Greve I, Mairbaurl H, Bartsch P:* Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. *Jama* 287: 2228–2235, 2002.
18 *Sartori C, Allemann Y, Trueb L, Delabays A, Nicod P, Scherrer U:* Augmented vasoreactivity in adult life associated with perinatal vascular insult. *Lancet* 353: 2205–2207, 1999.
19 *Sartori C, Allemann Y, Trueb L, Lepori M, Maggiorini M, Nicod P, Scherrer U:* Exaggerated pulmonary hypertension is not sufficient to trigger high-altitude pulmonary oedema in humans. *Schweiz Med Wochenschr* 130: 385–389, 2000.
20 *Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, Hutter D, Turini P, Hugli O, Cook S, Nicod P, Scherrer U:* Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med* 346: 1631–1636, 2002.
21 *Sartori C, Duplain H, Lepori M, Egli M, Maggiorini M, Nicod P, Scherrer U:* High altitude impairs nasal transepithelial sodium transport in HAPE-prone subjects. *Eur Respir J* 23: 916–920, 2004.
22 *Bartsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O:* Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med* 325: 1284–1289, 1991.
23 *Richalet JP, Gratadour P, Robach P, Pham I, Dechaux M, Joncquiert-Latarjet A, Mollard P, Brugniaux J, Cornolo J:* Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. *Am J Respir Crit Care Med* 171: 275–281, 2005.
24 *Ghofrani HA, Reichenberger F, Kohstall MG, Mrosek EH, Seeger T, Olschewski H, Seeger W, Grimminger F:* Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: a randomized, double-blind, placebo-controlled crossover trial. *Ann Intern Med* 141: 169–177, 2004.
25 *Allemann Y, Saner H, Meier B:* High altitude stay and air travel in coronary heart disease. *Schweiz Med Wochenschr* 128: 671–678, 1998.