

Review

High altitude-induced pulmonary oedema

Marco Maggiorini *

Intensive Care Unit, Department of Internal Medicine, University Hospital, Rämistrasse 100, CH-8091 Zürich, Switzerland

Received 6 June 2006; received in revised form 27 June 2006; accepted 3 July 2006

Available online 12 July 2006

Time for primary review 12 days

Abstract

Almost one mountain trekker or climber out of two develops several symptoms of high altitude illness after a rapid ascent (>300 m/day) to an altitude above 4000 m. Individual susceptibility is the most important determinant for the occurrence of high altitude pulmonary oedema (HAPE). Symptoms associated with HAPE are incapacitating fatigue, chest tightness, dyspnoea at the slightest effort, orthopnoea, and cough with due to haemoptysis in an advanced stage of the disease pink frothy sputum. The hallmark of HAPE is an excessively elevated pulmonary artery pressure (mean pressures of 35 and 55 mm Hg), which precedes the development of pulmonary oedema. Elevated pulmonary capillary pressure and protein- as well as red blood cell-rich oedema fluid without signs of inflammation in its early stage are characteristic findings. Furthermore, decreased fluid clearance from the alveoli may contribute to this non-cardiogenic pulmonary oedema. Immediate descent or supplemental oxygen and nifedipine are recommended until descent is possible. Susceptible individuals can prevent HAPE by slow ascent: an average gain of altitude not exceeding 400 m/day above an altitude of 2500 m. If progressive high altitude acclimatization is not possible, a prophylaxis with nifedipine should be recommended.

© 2006 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.

Keywords: High altitude pulmonary oedema; Capillary pressure; Hypoxic pulmonary vasoconstriction; *Trans*-epithelial Na transport; Nifedipine; Tadalafil; Dexamethasone

1. Introduction

Two forms of high altitude illness can be distinguished: a cerebral form called acute mountain sickness (AMS) and a pulmonary form called high altitude pulmonary oedema (HAPE). Altitude, the rate of ascent, and individual susceptibility in particular are the major determinants of AMS and HAPE in mountaineers and trekkers. At an intermediate altitude such as in Colorado, the prevalence of AMS among visitors is estimated at 25% [1]. Among trekkers in the Himalayas and mountaineers in the Alps ascending at a rate of >600 m/day, the prevalence of AMS at altitudes between 4000 m and 5600 m is 30–60% [2–8]. In contrast to AMS, HAPE is less frequent. The estimated incidence of HAPE in visitors to ski resorts in the Rocky Mountains of Colorado is 0.01–0.1% [9]. In a general alpine mountaineering population, the prevalence of HAPE is <0.2% [10]. The HAPE incidence among trekkers in the

Himalayas and climbers in the Alps ascending at a rate of >600 m/day is around 4% [3,11]. In the alpine setting, when an altitude of 4559 m was reached within 22 h, the incidence increased to 7% in mountaineers without a history of radiographically documented HAPE and to 62% in mountaineers with such a history [12]. In an unselected population of Indian soldiers, airlift to an altitude of 5500 m was associated with a HAPE incidence of up to 15% [13].

2. Clinical presentation

2.1. Clinical examination

HAPE presents within 2–5 days after arrival at high altitude [13–15]. It is rarely observed below altitudes of 2500–3000 m and after 1 week of acclimatization at a particular altitude. Early symptoms of HAPE include exertional dyspnoea, cough, and suddenly reduced exercise performance. As pulmonary oedema progresses, orthopnoea, breathlessness at rest, and gurgling in the chest develop, cough worsens, and pink frothy

* Tel.: +41 44 255 22 04; fax: +41 44 255 31 81.

E-mail address: klinmax@usz.unizh.ch.

Table 1
Clinical and radiographic findings in adults without and with HAPE

	HAPE- (n=120)		HAPE+ (n=30)	
	AMS- (n=87)	AMS+ (n=33)	AMS- (n=9)	AMS+ (n=21)
Rales+ /++ (%)	7 (8)	5 (15)	3 (33)	8 (38)
Body temperature (°C)	36.8 (36.6–36.9)	37.2 (37.0–37.4) ^a	37.1 (36.9–37.4) ^b	37.7 (37.5–37.9) ^{a,c}
Clin. AMS score	1.9 (1.6–2.3)	4.9 (4.4–5.5) ^a	2.7 (1.3–4.0)	7.3 (6.4–8.3) ^{a,c}
Rad. score	0.3 (0.2–0.5)	0.3 (0.1–0.6)	6.7 (3.5–9.9) ^b	7.1 (5.3–8.8) ^c
PaO ₂	45 (43–46)	40 (38–42) ^a	37 (32–42) ^b	33 (30–35) ^c
PaCO ₂	26 (25–27)	28 (27–29)	27 (25–29)	27 (25–28)
AaDO ₂	5.2 (3.9–6.4)	7.1 (5.1–7.1)	12.1 (7.3–16.9) ^b	15.6 (12.4–18.4) ^c

Mean (95% confidence intervals) of clinical (clin.) and radiographic (rad.) scores, arterial (a) PO₂, PCO₂, and the alveolar–arterial difference for oxygen (AaDO₂) in 60 adults examined after ascent to 4559 m and a stay for 3 consecutive days. A total of 150 examinations were performed, and in 30 of them chest radiography was compatible with the diagnosis of HAPE.

These results were obtained in collaboration with P. Bärtsch and O. Oelz.

^a $p < 0.01$ vs. AMS- in the HAPE-/+ groups.

^b $p < 0.01$ vs. AMS- in the HAPE- group.

^c $p < 0.01$ vs. AMS+ in the HAPE- group.

sputum reveals overt pulmonary oedema [13–15]. The clinical examination shows cyanosis, tachypnoea, tachycardia, and frequently body temperature > 37.5 °C [16]. Râles are discrete at the beginning, typically located over the middle lung fields [13–15]. Often, there is a discrepancy between the minor findings at auscultation compared with the widespread disease on the chest radiograph [17] (Table 1). In advanced cases, signs of concomitant severe AMS with ataxia and decreased levels of consciousness – signs of high altitude cerebral oedema – may develop [18,19] (Table 1).

2.2. Chest radiography and laboratory analyses

Chest radiographs and CT-scans of early HAPE show a patchy, peripheral distribution of oedema as shown in Fig. 1. The radiographic appearance of HAPE is more homogeneous and diffuses in advanced cases and during recovery [20]. The results of arterial blood gas, radiographic score,

and AMS score obtained in 19 adults with HAPE at 4559 m (Table 1) demonstrate that HAPE may develop with nearly no symptoms of AMS (6/19) and that the extension of pulmonary infiltrates does correlate with the impairment of gas exchange. In advanced cases of HAPE observed at an altitude of 4559 m, arterial PO₂ likely drops below the 35 mm Hg mark.

There are no characteristic findings in common laboratory examinations with the exception of moderately elevated C-reactive protein (< 100 mg/l) [13,15,21]. In the early stage of HAPE broncho-alveolar lavage (BAL) reveals a protein- and red blood cell-rich oedema fluid without signs of inflammation [22], whereas in a more advanced stage pro-inflammatory mediators and granulocytes add to the initial changes [15,23]. Autopsies showed diffuse pulmonary oedema with bloody foamy fluid present in the airways and signs of inflammation involving the alveoli and the capillaries [24,25].

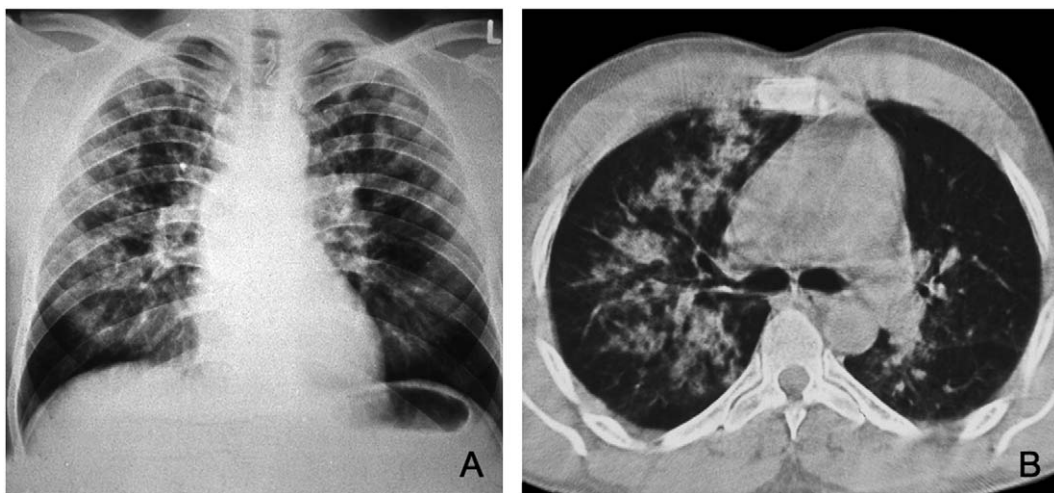


Fig. 1. Chest radiograph and CT-scan in a mountaineer with HAPE. Radiograph of a male patient with HAPE showing patchy distributed infiltrates over the whole lung (A). The CT-thorax of the same patient shows a patchy distribution of oedema, localized predominately around the right hilus (B). (These illustrations were kindly provided by Dr. H. Fischer, Regional Hospital Visp, Switzerland.)

2.3. Right heart catheter studies

Since the first hemodynamic measurements performed in patients with HAPE admitted to hospital we know that HAPE is associated with elevated pulmonary artery pressure [14,26–29]. In a prospective hemodynamic evaluation of HAPE-susceptible adults performed after rapid ascent to 4559 m within 24 h, mean pulmonary artery pressure increased to 38 mm Hg (range 28–42 mm Hg) [30] (Fig. 2). In those who developed pulmonary oedema during that occasion, mean pulmonary artery pressure was 42 mm Hg (range 36–51 mm Hg). Moreover, all these studies consistently show that in HAPE, left ventricular filling pressures, as assessed by the measurement of pulmonary occluded pressure (wedge pressure), right atrial pressure, and cardiac output are normal [28–30]. Thus, hemodynamic evaluations in HAPE clearly indicate that the development of pulmonary hypertension within hours after rapid exposure to high altitude is a hallmark of this disease. This is further supported by those studies indicating that HAPE is prevented or treated by the use of pulmonary vasodilators [31–33].

3. Pathophysiology

3.1. Exaggerated hypoxic pulmonary vasoconstriction

Oxygen sensors located in the pulmonary vasculature detect the drop of alveolar oxygen tension and lead to vasoconstriction of small pulmonary arteries [34,35] and pulmonary veins [36]. The response of smooth-muscle cells in the pulmonary vasculature to acute hypoxia begins within seconds and involves inhibition of voltage-dependent potassium channels, membrane depolarization, and calcium entry through L-type calcium channels [35,37]. Moreover, hypoxia up-regulates transient receptor potential channels, leading to additional calcium entry through receptor and store-operated calcium-channels [35]. Whether a

constitutively decreased mRNA expression of voltage-dependent potassium channels or an acquired transcriptional defect of the voltage-dependent potassium channels protein expression is at the origin of HAPE susceptibility remains to be determined.

Exaggerated hypoxic pulmonary vasoconstriction has been attributed to an increased susceptibility of the pulmonary circulation – sustained elevation of cytoplasmic calcium concentration – to sympathetic activity and/or high levels of endothelin-1. Increased sympathetic activity and elevated norepinephrine plasma levels have been found in individuals with AMS and HAPE [19,38–40]. Rapid exposure to 4559 m almost doubles plasma endothelin-1 levels [41], the highest values being measured in individuals with HAPE [42]. Both intensity of sympathetic activity [40] and plasma endothelin-1 levels are positively correlated with systolic pulmonary artery pressure [41,42].

Endothelium-mediated vasodilatation is crucial for the control of pulmonary vasoconstriction. Hypoxia-induced endothelial dysfunction resulting in an impaired endothelium-dependent vasodilatation in the systemic circulation [43] and an impaired nitric oxide production in the lung [22,44,45] could be another mechanism leading to elevated pulmonary artery pressure in HAPE-susceptible individuals. In fact, upon acute exposure to hypoxia, exhaled nitric oxide concentrations [44,45] and nitrite/nitrate concentrations in the BAL fluid [22] tend to decrease in individuals prone to HAPE, whereas they increase in those resistant to the condition. Moreover, in susceptible individuals the prophylactic intake of tadalafil, a phosphodiesterase-5 inhibitor, prevents high altitude pulmonary hypertension and HAPE [33].

Taken together, the results of all these studies indicate that an imbalance between hypoxia-mediated vasoconstriction and impaired nitric oxide bioavailability is the provable mechanism behind the elevated pulmonary artery pressure in HAPE-susceptible individuals. Whether ethnic differences between Caucasians [46] and Japanese [47] for endothelial nitric oxide polymorphism may also contribute to HAPE susceptibility remains to be established.

3.2. Elevated pulmonary capillary pressure

During hemodynamic measurements performed in HAPE-susceptible and non-susceptible adults at 4559 m, we estimated the pulmonary capillary pressure using the arterial occlusion method [30], which most likely measures pressures in vessels close to 100 μ m in diameter [48] and demonstrated that the pulmonary capillary pressure is elevated in HAPE. Pulmonary capillary pressure was on average 16 mm Hg (range 14–18 mm Hg) in HAPE-susceptible subjects without pulmonary oedema and 22 mm Hg (range 20–26 mm Hg) in those who developed HAPE [30] (Fig. 3). This result suggests that in adults, the pulmonary capillary pressure threshold value for oedema formation is 20 mm Hg, which is in keeping with previous experimental observations in dogs indicating a PO_2 -independent critical capillary pressure of 17 to 24 mm Hg, above which the lungs continuously gain weight [49,50].

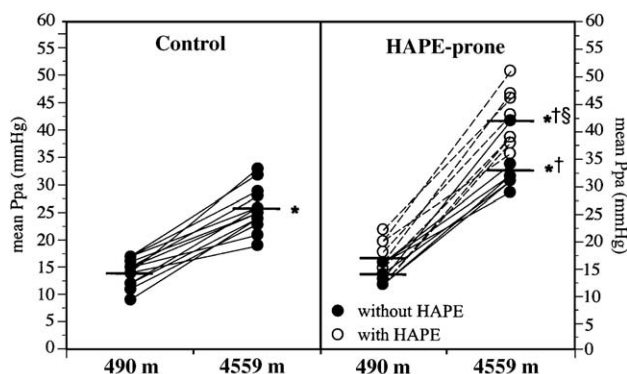


Fig. 2. Changes in mean pulmonary artery pressure from low to high altitude. Individual mean pulmonary artery pressures (Ppa) measured at 4559 m in HAPE-resistant (control) and HAPE-prone (susceptible) adults [30]. The closed dots indicate mean Ppa in individuals without radiographic evidence of HAPE. The open dots indicate those individual subjects who developed HAPE during the 2 days' stay at 4559. The horizontal bars (—) indicate median Ppa value for each group of subjects. * $p < 0.01$ vs. 490 m, † $p < 0.01$ vs. control, ‡ $p < 0.01$ vs. HAPE-susceptible adults without HAPE.

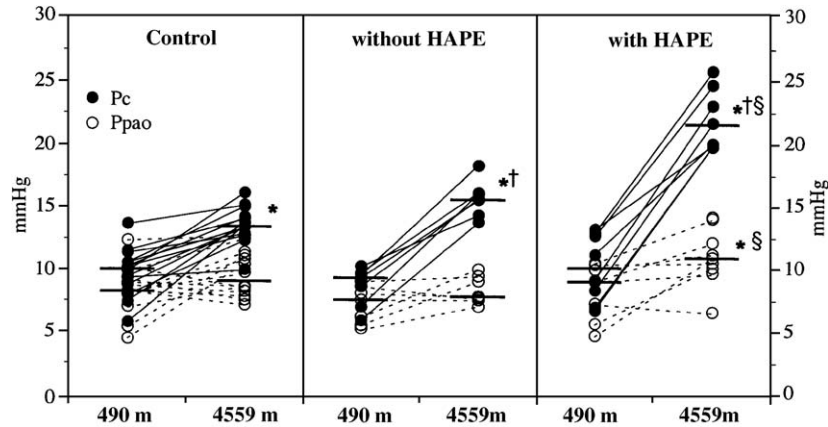


Fig. 3. Changes in pulmonary capillary pressure and pulmonary artery occlusion pressure upon ascent to 4559 m. Individual pulmonary capillary pressure (Pc) and pulmonary artery occlusion pressure (Ppao=wedge pressure), assessed using the arterial occlusion technique, in controls, and HAPE-susceptible subjects without and with pulmonary oedema [30]. The Pc is indicated by the filled dots and Ppao values by the open dots. The figure shows that in subjects who develop HAPE, the Pc was higher than 19 mm Hg and that the increase in Ppao, although significant, is minimal. The horizontal bars (—) indicate median Ppa value for each group of subjects. * $p < 0.01$ vs. 490 m, † $p < 0.01$ vs. control, ‡ $p < 0.01$ vs. HAPE-susceptible adults without HAPE.

There are two possible mechanisms leading to an elevated pulmonary capillary pressure in subjects susceptible to HAPE: a heterogeneous distribution of pulmonary blood flow within the pulmonary vascular bed [51,52] or a hypoxic constriction occurring at the level of the pulmonary veins [36,53]. A heterogeneous distribution of blood flow within the pulmonary circulation causing regional over-perfusion of capillaries, i.e. in areas with the least arterial vasoconstriction [51], is suggested by the results of a recent study obtained using a functional magnetic resonance imaging technique (arterial spin labelling) in a small number of volunteers exposed to hypoxia, indicating an increased pulmonary blood flow heterogeneity in HAPE-susceptible individuals [52]. Non-uniformly distributed blood flow in hypoxia was also found using the fluorescent microspheres technique in pigs [54] and dogs [55]. Non-homogeneous distribution of blood flow could be caused by uneven distribution of alveolar ventilation, hence hypoxic vasoconstriction [56] or heterogeneous oxygen sensing within smooth muscle cells of the pulmonary vascular tree [57–59]. On the other hand there is good evidence that pulmonary veins contract in response to hypoxia [36,60,61], increasing the resistance downstream of the region of fluid filtration [62], which suggests that HAPE could develop even in the absence of a heterogeneous distribution of pulmonary blood flow within the pulmonary vascular bed. Moreover, markedly increased pulmonary artery pressure in hypoxia may also cause transvascular leakage of small arterioles [63]. However, the patchy distribution of pulmonary infiltrates on chest radiographs and CT scans of the lungs found in individuals with HAPE (Fig. 1) strongly support the heterogeneous distribution of elevated capillary pressures within the permeable region of the pulmonary circulation, which in summary is likely to rely on an unevenly distributed hypoxic vasoconstriction in either pulmonary arteries or veins, or both.

3.3. High-permeability type of oedema

Broncho-alveolar lavage (BAL) performed in HAPE-susceptible adults within a day after ascent to 4559 m revealed elevated red blood cell counts and serum-derived protein concentration in BAL fluid [22]. The number of red blood cells/ μl and the albumin concentration was higher in those individuals with HAPE at the time of BAL than in those who developed it within the next 24 h. The threshold for the increase in albumin and red blood cells was at a systolic pulmonary artery pressure of approximately 35 mm Hg and 60 mm Hg, respectively (Fig. 4). The number of alveolar macrophages/ μl and neutrophils/ μl and the concentration of the pro-inflammatory mediators interleukin-1 (IL-1), TNF- α ,

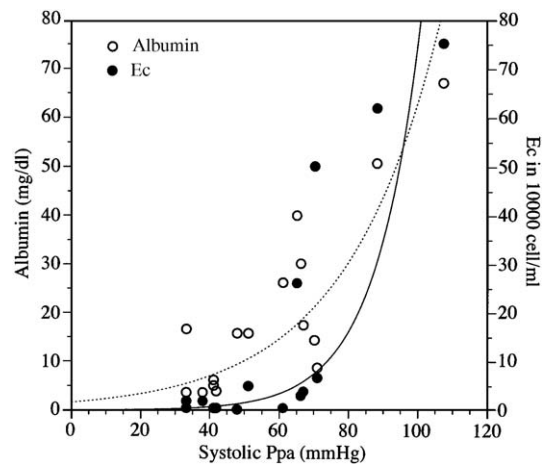


Fig. 4. Relationship between systolic pulmonary artery pressure and BAL red blood cell count and albumin concentration. Individual broncho-alveolar lavage (BAL) red blood cell and albumin concentration plotted against systolic pulmonary artery pressure (sPpa) at high altitude (4559 m). The figure shows that the threshold sPpa for the appearance in the BAL fluid of albumin was 35 mm Hg and that for red blood cells was 60 mm Hg [22].

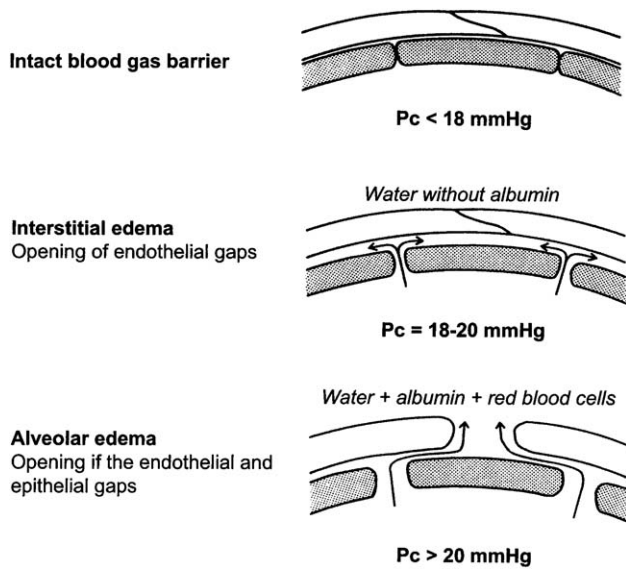


Fig. 5. Mechanism of pulmonary capillary leak in HAPE. Elevated pulmonary capillary pressure (Pc) cause progressive distension of the vessel wall leading to opening of endothelial and epithelial gaps through which first proteins and later red blood cells leak into the alveolar space.

IL-8, thromboxane, prostaglandin E₂, and leukotriene B₄ (LTB₄), was not increased. These results are in line with studies showing that in rabbit lungs, elevated pulmonary vascular pressure causes injury to both the alveolar epithelial and the capillary endothelial cells, resulting in a protein- and red blood cell-rich lung oedema fluid [64–66] (Fig. 5). Thus, HAPE in its early stage is a high pressure-mediated permeability type of pulmonary oedema.

BAL fluid examination in adults with advanced HAPE show also elevated levels of pro-inflammatory cytokines and LTB₄ [23,67], suggesting secondary inflammation to the high-pressure injury to the blood–gas barrier and/or lung oedema formation. Elevated concentrations of pro-inflammatory cytokines found in patients with cardiogenic pulmonary oedema [68,69] support this concept. A release of pro-inflammatory cytokines [69] continuing for several days after normalization of the pulmonary artery pressure may be the origin of a prolonged respiratory failure described in some individuals [70].

3.4. Reduced fluid clearance from the alveolar space

Studies performed in cell cultures and rats exposed to hypoxia indicate that hypoxia inhibits the activity and the expression of alveolar epithelial cell sodium (Na⁺) transporters, particularly the apical membrane epithelial Na⁺ channel (ENaC) and the basolateral membrane Na⁺/K⁺-ATPase, and hence the Na⁺ transport and associated alveolar fluid clearance across the alveolar epithelial membrane [71–74] (Fig. 6). Since alveolar epithelium is not accessible in humans, nasal epithelium, which has Na⁺ transporters that are similar to those of the alveolar epithelium, is used to estimate alveolar epithelium Na⁺ transport activity [75]. Accordingly, hypoxia was found to inhibit nasal epithelial Na⁺ transport in both HAPE-

resistant and -susceptible mountaineers [76,77]. Moreover, at low altitude, HAPE-susceptible adults present a lower activity of the ENaC compared to HAPE-resistant individuals [76–78], suggesting a possible contribution of ENaC to the pathophysiology of HAPE.

β₂-Receptor agonists have been shown to stimulate alveolar epithelial Na⁺ and fluid transport in rats exposed to hypoxia [74] and pulmonary oedema reabsorption in patients with acute respiratory distress syndrome [79]. The prophylactic inhalation of a high dose (2 × 125 μg) of salmeterol decreased the incidence of HAPE from 74% to 33% [78]. Thus, it is possible that a decreased activity of Na⁺ transporters, particularly the ENaC, across the alveolar epithelial membrane will be part of the pathophysiologic mechanism of HAPE. On the other hand, one cannot exclude that the effect of aerosolized salmeterol prophylaxis may be attributed to other actions of the drug [80,81]. Treatment with a β₂-agonist may cause vasodilatation by an increase in nitric oxide production [82], inhibition of endothelial cell contraction, and reduction in intercellular gaps [83–85]. Moreover, β₂-agonists also have a clear anti-inflammatory effect by reducing neutrophil influx and degranulation and the accumulation of TNF-α in the alveolar airspaces [86]. Thus, to really test the role of Na⁺ transporters in HAPE, more specific drugs are needed.

4. Factors contributing to lung oedema formation

4.1. AMS and hypoxemia

AMS is not a precondition for the development of HAPE. This is suggested by epidemiological studies indicating a 7- to 8-fold higher incidence of AMS than HAPE [3,11]

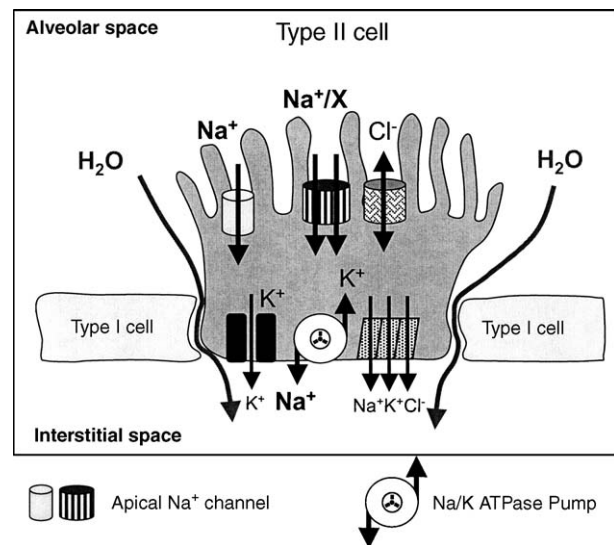


Fig. 6. Alveolar epithelial cell fluid reabsorbing mechanism. Alveolar epithelial apical and basolateral membrane ion channels and exchangers involved in active transepithelial sodium and water absorption. There is an active reabsorption of sodium; water and chloride follow passively. Acute hypoxia reduces alveolar fluid clearance by inhibition of apical sodium entry pathways and basolateral Na⁺/K⁺-ATPase activity.

and by the observation that HAPE may develop even in the absence of AMS [17] (Table 1). On the other hand, it is likely that severe AMS may be a risk factor for HAPE. This is suggested by studies indicating that individuals with severe AMS have a low PaO₂ (Table 1) [87,88] and/or a low hypoxic ventilatory drive. A low hypoxic ventilatory drive is known to possibly increase susceptibility to HAPE [89–91]; however, the considerable overlap between HAPE-susceptible and -resistant individuals suggests that it is at best permissive but not compulsory regarding susceptibility to HAPE.

4.2. Airway infections

It is conceivable that any process enhancing the permeability of the alveolar-capillary barrier decreases the pulmonary capillary pressure threshold above which pulmonary oedema develops. Increased lung fluid accumulation during hypoxic exposure after priming rats with endotoxins or viruses [92] and the reported association of preceding viral infections (predominantly of the upper respiratory tract) and HAPE in children visiting Colorado [93] support this concept. Thus, a variable pulmonary capillary permeability between high altitude exposures could tentatively explain why in HAPE-susceptible individuals the reoccurrence rate of pulmonary oedema after rapid ascent to high altitude is not 100%.

4.3. Congenital anomalies

Restriction of the pulmonary vascular bed cross-sectional area may also contribute to increase pulmonary artery pressure upon exposure to high altitude. This theory is supported by reports indicating that congenital anomalies of the large pulmonary arteries [94,95] and pulmonary embolism [96,97] are associated with an increased risk to develop HAPE even at altitudes below 3000 m. Moreover, small lungs relative to body size have also been retained as a possible risk factor for HAPE [56,98].

At risk for HAPE at a moderate altitude are also patients with congenital cardiac shunts [99] and/or pre-existing pulmonary hypertension [100]. A right–left shunt across a patent foramen ovale may exacerbate high altitude hypoxemia and hence lead to HAPE [101]. Thus, in patients who have developed HAPE at altitudes below 3000 m, echocardiography is recommended to exclude pulmonary hypertension and a congenital anomaly.

4.4. Exercise

Strenuous exercise may also contribute to increasing pulmonary capillary pressure and hence the risk of HAPE. In fact, there is evidence that strenuous exercise causes subclinical permeability oedema with high red blood cells and protein concentrations that may last for more than a day at high altitude [102]. This may be caused by uneven distribution of blood flow across the pulmonary vascular bed [56] and/or elevated pulmonary vascular pressures [103,104]. In normoxia and

hypoxia, strenuous exercise causes pulmonary blood flow and pulmonary vascular pressures to increase by a large extent, the increase in vascular pressure being essentially related to the upstream transmission of increased left atrial pressure, and the increase in pulmonary vascular resistance being less important [103,104]. In HAPE-susceptible adults, exercise increases pulmonary artery pressure and pulmonary artery occluded pressure (wedge pressure) more than in HAPE-resistant individuals [105], which could be at least in part attributed to an impaired left ventricular filling because of the dilation of the right ventricle and bulging of the septum toward the left side [106].

5. Prevention

5.1. Slow ascent

Slow ascent is the major measure of prevention that is effective even in susceptible individuals. In contrast to AMS, there are no studies prospectively investigating the incidence of HAPE according to the rate of ascent. Indirect evidence has come from the observation that even subjects who developed HAPE more than once upon rapid ascent in the Alps successfully reached altitudes up to 7000 m when the average daily ascent rate above 2000 m does not exceed 350–400 m/day [107]. Climbers with any symptoms of AMS or beginning HAPE should be advised not to ascend further and to avoid vigorous exercise during the first days of exposure to altitudes above 3000 m, since exercise may enhance or cause pulmonary oedema [102,105]. Furthermore, susceptibility to HAPE may be increased during and shortly after infection [93].

5.2. Drug prevention

Prevention of an excessive rise in pulmonary artery pressure is the standard for the prevention of HAPE in individuals with a positive history of HAPE when slow ascent is not possible. The calcium channel blocker nifedipine acts as a vasodilator on both the pulmonary and the systemic circulation, although at high altitude with sympathetic activation the systemic vasodilatory effect is negligible. 20 mg nifedipine of the slow-release formulation taken every 8 h starting 24 h before ascent to 4559 m and continued until descent decreased the incidence of HAPE from 63% to 10%. Recently, these results could be reproduced using 10 mg tadalafil bid, a phosphodiesterase-5 inhibitor [33]. The incidence of HAPE was 74% in the placebo and 10% in the tadalafil group. However, it should be underlined that both nifedipine and tadalafil are not effective in preventing AMS [33,91], and that in some susceptible individuals phosphodiesterase-5 inhibitors may possibly exacerbate AMS by unknown mechanism [108]. No other significant side effects were reported for either drug [32,33]. Thus, a pulmonary vasodilator should be given for HAPE prevention only, starting with the ascent and ending when acclimatization is completed. If AMS is present despite pulmonary vasodilator prophylaxis, additional acclimatization or AMS prophylaxis with acetazolamide is recommended

[109,110]. Whether acetazolamide prophylaxis prevents HAPE is yet unknown, but recent results suggest that this could be the case. In fact, in animals exposed to acute hypoxia, acetazolamide inhibited hypoxic pulmonary vasoconstriction [111,112].

The use of the β_2 -agonist salmeterol has been suggested as an alternative for the prophylaxis of HAPE in susceptible adults. Salmeterol inhaled at the high dose of 125 μg bid during rapid ascent to 4559 m followed by a two-night stay decreased the incidence of HAPE from 74% to 33% [78], thus slightly less than a pulmonary vasodilator, suggesting that preventing an excessive increase in pulmonary artery pressure is possibly more effective. Therefore, the routine use of salmeterol for HAPE prophylaxis cannot be recommended until a clinical trial proves equivalence between salmeterol and a pulmonary vasodilator.

Interestingly, recent preliminary data indicate that prophylaxis with dexamethasone, which has been proven effective in the prevention and treatment of AMS [113,114], prevents HAPE in susceptible adults when taken 1 day prior to ascent and continued during ascent and stay at 4559 m [33]. Surprisingly, in this study we found that dexamethasone significantly attenuated the increase in pulmonary artery pressure at high altitude, its effect being comparable to that observed in a second group of HAPE-susceptible participants receiving tadalafil. This effect can tentatively be explained by a dexamethasone-mediated stimulation of cGMP production in hypoxia [115], an increase in the activity of nitric oxide synthase [116], and a favourable modulation of the increased sympathetic activity in these individuals [38,40,117]. However, other mechanisms may also account for the effect of dexamethasone such as an improvement of the alveolar *trans*-epithelial Na^+ and water transport [118], tightening of the pulmonary capillary endothelium [119] possibly by inhibition of hypoxia-induced inflammation [120], and improvement of surfactant production [121,122]. Although prophylaxis with dexamethasone for individuals susceptible to HAPE and AMS appears attractive, before general recommendation can be given further studies are needed to determine the minimal effective dose, its best route of administration (topical vs. systemic) and its safety profile in the setting of mountaineering.

6. Treatment

Immediate improvement of oxygenation either by supplemental oxygen, hyperbaric treatment [123,124], or by rapid descent is the treatment of choice for HAPE. For the mountaineer in a remote area without medical care, descent has first priority, while the tourist with HAPE visiting a high altitude plateau in the Andes, Himalayas, or Rocky Mountains may stay at altitude if medical facilities are available. If it takes a few days in a remote area to reach lower altitude, treatment with nifedipine is strongly recommended. In mountaineers with HAPE at 4559 m, treatment with 20 mg slow-release nifedipine taken every 6 h led to a persistent relief of symptoms, improvement of gas exchange, and radiographic clearance over an observational period of 34 h [31]. In this

study, nifedipine therapy was not associated with hypotension. To date, there are no clinical trials on the use of more selective pulmonary vasodilators such as sildenafil or other phosphodiesterase-5 inhibitors in this setting. In an area where medical infrastructure and assistance are available, vasodilatory treatment is not strictly necessary because with bed-rest and supplemental oxygen for 24 to 48 h, relief of symptoms is achieved within hours and complete clinical recovery within several days while staying at the same altitude [125]. Whether the combined treatment of bed-rest, supplemental oxygen, and nifedipine or other vasodilator is superior to bed-rest and oxygen alone has not yet been investigated. In adults with advanced HAPE, intermittent, continuous, positive end-expiratory airway pressure has been shown to improve SaO_2 by 10–20% [126,127]; however, one should be aware that it might cause high altitude cerebral oedema by increasing central venous pressure [128].

7. Summary

HAPE develops in non-acclimatized mountaineers after rapid ascent to altitudes above 2500 m. Besides rapid ascent, individual susceptibility is the major risk factor, with the occurrence in individuals with a previous HAPE episode being 60–70% after ascent to 4559 m within 24 h. HAPE usually develops within the first 4–5 days at altitude and presents with cough, dyspnoea, and tachycardia, and in its advanced stage with orthopnoea and pink sputum. Chest radiography reveals patchy distributed pulmonary infiltrates. Laboratory exams show severe hypoxemia and, in its late stage, a slightly elevated c-reactive protein plasma level.

HAPE is a non-cardiogenic type of pulmonary oedema most probably caused by excessively elevated pulmonary artery pressure and pulmonary capillary pressure that lead to a permeability type of pulmonary oedema. In its early stage pulmonary oedema fluid is rich in red blood cells, and the albumin concentration is elevated. Pro-inflammatory mediators are found only in an advanced stage, suggesting secondary inflammation. Impaired alveolar epithelial Na^+ transport, and hence alveolar fluid clearance, may add to the accumulation of oedema in the alveoli. A heterogeneous distribution of hypoxic pulmonary vasoconstriction with consequent over-perfusion of unprotected pulmonary capillaries and/or a hypoxic constriction of pulmonary veins are the possible mechanisms leading to elevated pulmonary capillary pressure. Congenital anomalies of the pulmonary circulation, restriction of the pulmonary vascular bed, and strenuous exercise may further add to increased pulmonary capillary pressure. Preceding or concomitant infection may favour HAPE development, increasing pulmonary capillary permeability.

For the prevention of HAPE, slow ascent (<400 m/day) is strongly recommended. If this is not possible, prophylaxis with vasodilators such as nifedipine or tadalafil has been shown to be effective. Recently, in a small randomised, placebo-controlled trial, dexamethasone taken 24 h before ascent prevented excessive elevation of pulmonary artery pressure and HAPE. In

easily accessible areas, HAPE has been successfully treated with supplemental oxygen and bed-rest, followed by a descent to lower altitude. In more remote areas, the use of nifedipine and oxygen are strongly recommended.

References

- [1] Montgomery AB, Millis J, Luce JM. Incidence of acute mountain sickness at intermediate altitude. *JAMA* 1989;261:732–4.
- [2] Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet* 1976;2(7996):1149–54.
- [3] Maggiorini M, Bühler B, Walter M, Oelz O. Prevalence of acute mountain sickness in the Swiss Alps. *BMJ* 1990;301:853–5.
- [4] Ziaee V, Yunesian M, Ahmadijad Z, Halabchi F, Kordi R, Alizadeh R, et al. Acute mountain sickness in Iranian trekkers around Mount Damavand (5671 m) in Iran. *Wilderness Environ Med* 2003 (Winter);14:214–9.
- [5] Basnyat B, Lemaster J, Litch JA. Everest or bust: a cross sectional, epidemiological study of acute mountain sickness at 4243 meters in the Himalayas. *Aviat Space Environ Med* 1999;70:867–73.
- [6] Schneider M, Bernasch D, Weymann J, Holle R, Bartsch P. Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate. *Med Sci Sports Exerc* 2002;34:1886–91.
- [7] Gaillard S, Dellasanta P, Loutan L, Kayser B. Awareness, prevalence, medication use, and risk factors of acute mountain sickness in tourists trekking around the Annapurnas in Nepal: a 12-year follow-up. *High Alt Med Biol* 2004;5:410–9.
- [8] Pesce C, Leal C, Pinto H, Gonzalez G, Maggiorini M, Schneider M, et al. Determinants of acute mountain sickness and success on Mount Aconcagua (6962 m). *High Alt Med Biol* 2005;6:158–66.
- [9] Sophocles Jr AM. High-altitude pulmonary edema in Vail, Colorado, 1975–1982. *High Alt Med Biol* 1986;144:569–73.
- [10] Hochstrasser J, Nanzer A, Oelz O. Altitude edema in the Swiss Alps. Observations on the incidence and clinical course in 50 patients 1980–1984. *Schweiz Med Wochenschr* 1986;116:866–73.
- [11] Hackett PH, Rennie D. Rales, peripheral edema, retinal hemorrhage and acute mountain sickness. *Am J Med* 1979;67:214–8.
- [12] Bärtsch P, Vock P, Maggiorini M, Francioli M, Fretz C, Schobersberger W, et al. Respiratory symptoms, radiographic and physiologic correlations at high altitude. In: Decker, editor. *Phyladelphia. Hypoxia: The Adaptation*: JR Sutton, G Coates, JE Remmers; 1990.
- [13] Singh I, Roy SB. High altitude pulmonary edema: clinical, hemodynamic, and pathologic studies. In: Command UARaD, editor. *Biomedicine of high terrestrial elevation problems*; 1969. p. 108–20. Washington D.C.
- [14] Hultgren NH, Lopez CE, Lundberg E, Miller H. Physiologic studies of pulmonary edema at high altitude. *Circulation* 1964;29:393–408.
- [15] Kobayashi T, Koyama S, Kubo KMF, Kusama S. Clinical features of patients with high altitude pulmonary edema in Japan. *Chest* 1987;92:814–21.
- [16] Maggiorini M, Bärtsch P, Oelz O. Association between raised body temperature and acute mountain sickness: a cross sectional study. *BMJ* 1997;315:403–4.
- [17] Vock P, Fretz C, Francioli M, Bärtsch P. High altitude pulmonary edema: findings at high altitude chest radiography and physical examination. *Radiology* 1989;170:661–6.
- [18] Houston CS, Dickinson J. Cerebral form of high-altitude illness. *Lancet* 1975;2:758–61.
- [19] Koyama S, Kobayashi T, Kubo K, Fukushima M, Yoshimura K, Shibamoto T, et al. The increased sympathoadrenal activity in patients with high altitude pulmonary edema is centrally mediated. *Jpn J Med* 1988;27:10–6.
- [20] Vock P, Brutsche MH, Nanzer A, Bärtsch P. Variable radiomorphologic data of high altitude pulmonary edema. *Chest* 1991;100:1306–11.
- [21] Kleger G-R, Bärtsch P, Vock P, Heilig B, Roberts LJ, Ballmer PE. Evidence against an increase in capillary permeability in subjects exposed to high altitude. *J Appl Physiol* 1996;81:1917–23.
- [22] Swenson S, Maggiorini M, Mongovin S, Gibbs S, Greve I, Maierbaurl H, et al. High altitude pulmonary edema is a non-inflammatory high permeability leak of the alveolar–capillary barrier. *JAMA* 2002;287:2226–35.
- [23] Schoene R, Hackett PH, Hederson WR, Sage EH, Chow M, Roach RC, et al. High altitude pulmonary edema. Characteristics of lung lavage fluid. *J Am Med Assoc* 1986;256:63–9.
- [24] Mosso A. *Fisiologia dell'uomo sulle alpi*. Milano: Fratelli Treves, Editori 1889.
- [25] Nayak NC, Roy S, Narayanan TK. Pathologic features of altitude sickness. *Am J Pathol* 1964;45:381–91.
- [26] Roy BS, Guleria JS, Khanna PK, Manchanda SC, Pande JN, Subba PS. Haemodynamic studies in high altitude pulmonary edema. *Br Heart J* 1969;31:52–8.
- [27] Penalzoa D, Sime F. Circulatory dynamics during high altitude pulmonary edema. *Am J Cardiol* 1969;23:368–78.
- [28] Kronenberg RG, Safar P, Wright F, Noble W, Wahrenbrock E, Hickey R, et al. Pulmonary artery pressure and alveolar gas exchange in men during acclimatization to 12,470 ft. *J Clin Invest* 1971;50:827–37.
- [29] Hultgren HN, Grover RF, Hartley LH. Abnormal circulatory responses to high altitude in subjects with a previous history of high-altitude pulmonary edema. *Circulation* 1971;44:759–70.
- [30] Maggiorini M, Mélot C, Pierre S, Pfeiffer F, Greve I, Sartori C, et al. High altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation* 2001;103:2078–83.
- [31] Oelz O, Maggiorini M, Ritter M, Waber U, Jenni R, Vock P, et al. Nifedipine for high altitude pulmonary oedema. *Lancet* 1989;2:1241–4.
- [32] Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high altitude pulmonary edema by nifedipine. *N Engl J Med* 1991;325:1284–9.
- [33] Maggiorini M, Brunner-La Rocca H-P, Bärtsch P, Fischler M, Böhm T, Bloch KE, et al. Dexamethasone and tadalafil prophylaxis prevents both excessive pulmonary constriction and high altitude pulmonary edema in susceptible subjects. *Eur Respir J* 2004;24(Suppl 28):S110.
- [34] Weir EK, Lopez-Barneo J, Buckler KJ, Archer SL. Acute oxygen-sensing mechanisms. *N Engl J Med* 2005;353:2042–55.
- [35] Murray F, Insel PA, Yuan JX. Role of O(2)-sensitive K(+) and Ca(2+) channels in the regulation of the pulmonary circulation: potential role of caveolae and implications for high altitude pulmonary edema. *Respir Physiol Neurobiol* 2006;151:192–208.
- [36] Gao Y, Raj JU. Role of veins in regulation of pulmonary circulation. *Am J Phys* 2005 (Feb);288:L213–26.
- [37] Remillard CV, Yuan JX. High altitude pulmonary hypertension: role of K⁺ and Ca²⁺ channels. *High Alt Med Biol* 2005;6:133–46.
- [38] Johnson TS, Rock PB, Young JB, Fulco CS, Trad LA. Hemodynamic and sympathoadrenal responses to altitude in humans: effect of dexamethasone. *Aviat Space Environ Med* 1988;59:208–12.
- [39] Bärtsch P, Shaw S, Francioli M, Gnädinger MP, Weidmann P. Atrial natriuretic peptide in acute mountain sickness. *J Appl Physiol* 1988;65:1929–37.
- [40] 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* 1999;99:1713–8.
- [41] Goerre S, Wenk M, Bärtsch P, Lüscher TF, Niroomand F, Hohenhaus E, et al. Endothelin-1 in pulmonary hypertension associated with high altitude exposure. *Circulation* 1995;90:359–64.
- [42] Sartori C, Vollenweider L, Löffler BM, Delabays A, Nicod P, Bartsch P, et al. Exaggerated endothelin release in high-altitude pulmonary edema. *Circulation* 1999;99:2665–8.
- [43] Berger MM, Hesse C, Dehnert C, Siedler H, Kleinbongard P, Bardenheuer HJ, et al. Hypoxia impairs systemic endothelial function in individuals prone to high-altitude pulmonary edema. *Am J Respir Crit Care Med* 2005;172:763–7.

- [44] Duplain H, Sartori C, Lepori M, Egli M, Allemann Y, Nicod P, et al. 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* 2000;162:221–4.
- [45] Busch T, Bartsch P, Pappert D, Grunig E, Hildebrandt W, Elser H, et al. Hypoxia decreases exhaled nitric oxide in mountaineers susceptible to high-altitude pulmonary edema. *Am J Respir Crit Care Med* 2001;163:368–73.
- [46] Weiss J, Haefeli WE, Gasse C, Hoffmann MM, Weyman J, Gibbs S, et al. Lack of evidence for association of high altitude pulmonary edema and polymorphisms of the NO pathway. *High Alt Med Biol* 2003;4:355–66.
- [47] Droma Y, Hanaoka M, Ota M, Katsuyama Y, Koizumi T, Fujimoto K, et al. Positive association of the endothelial nitric oxide synthase gene polymorphisms with high-altitude pulmonary edema. *Circulation* 2002;106:826–30.
- [48] Hakim TS, Kelly S. Occlusion pressures vs. micropipette pressures in the pulmonary circulation. *J Appl Physiol* 1989;67:1277–85.
- [49] Homik LA, Bshouty Z, Light RB, Younes M. Effect of alveolar hypoxia on pulmonary fluid filtration in in situ dog lungs. *J Appl Physiol* 1988;65:46–52.
- [50] Drake RE, Smith JH, Gabel JC. Estimation of the filtration coefficient in intact dog lungs. *Am J Physiol* 1980;238:H430–8.
- [51] Hultgren NH. High altitude pulmonary edema. In: Staub N, editor. Lung water and solute exchange. New York: Marcel Dekker; 1978. p. 437–64.
- [52] Hopkins SR, Garg J, Bolar DS, Balouch J, Levin DL. Pulmonary blood flow heterogeneity during hypoxia and high altitude pulmonary edema. *Am J Respir Crit Care Med* 2004;14:14.
- [53] Hillier SC, Graham JA, Hanger CC, Godbey PS, Glenny RW, Wagner Jr WW. Hypoxic vasoconstriction in pulmonary arterioles and venules. *J Appl Physiol* 1997;82:1084–90.
- [54] Hlastala MP, Lamm WJ, Karp A, Polissar NL, Starr IR, Glenny RW. Spatial distribution of hypoxic pulmonary vasoconstriction in the supine pig. *J Appl Physiol* 2004;96:1589–99.
- [55] Lamm WJ, Starr IR, Neradilek B, Polissar NL, Glenny RW, Hlastala MP. Hypoxic pulmonary vasoconstriction is heterogeneously distributed in the prone dog. *Respir Physiol Neurobiol* 2004;144:281–94.
- [56] Podolsky A, Eldridge MW, Richardson RS, Knight DR, Johnson EC, Hopkins SR, et al. Exercise-induced V_a/Q inequality in subjects with prior high-altitude pulmonary edema. *J Appl Physiol* 1996;81:922–32.
- [57] Walker BR. Evidence for uneven distribution of L-type calcium channels in rat pulmonary circulation. *Am J Physiol* 1995;269:H2051–6.
- [58] Weir EK, Reeve HL, Cornfield DN, Tristani-Firouzi M, Peterson DA, Archer SL. Diversity of response in vascular smooth muscle cells to changes in oxygen tension. *Kidney Int* 1997;51:462–6.
- [59] Yang XR, Lin MJ, Yip KP, Jeyakumar LH, Fleischer S, Leung GP, et al. Multiple ryanodine receptor subtypes and heterogeneous ryanodine receptor-gated Ca²⁺ stores in pulmonary arterial smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 2005;289:L338–48.
- [60] Raj JU, Chen P. Micropuncture measurement of microvascular pressures in isolated lamb lungs during hypoxia. *Circ Res* 1986;59:398–404.
- [61] Zhao Y, Packer CS, Rhoades RA. Pulmonary vein contracts in response to hypoxia. *Am J Physiol* 1993;265:L87–92.
- [62] Mitzner W, Sylvester JT. Hypoxic vasoconstriction and fluid filtration in pig lungs. *J Appl Physiol* 1981;51:1065–71.
- [63] Whayne Jr TF, Severinghaus JW. Experimental hypoxic pulmonary edema in the rat. *J Appl Physiol* 1968;25:729–32.
- [64] West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. *J Appl Physiol* 1991;70:1731–42.
- [65] Bachofen H, Schurch S, Weibel ER. Experimental hydrostatic pulmonary edema in rabbit lungs. Barrier lesions. *Am Rev Respir Dis* 1993;147:997–1004.
- [66] Bachofen H, Schurch S, Michel RP, Weibel ER. Experimental hydrostatic pulmonary edema in rabbit lungs. Morphology. *Am Rev Respir Dis* 1993;147:989–96.
- [67] Kubo K, Hanaoka M, Yamaguchi S, Hayano T, Hayasaka M, Koizumi T, et al. Cytokines in bronchoalveolar lavage fluid in patients with high altitude pulmonary edema at moderate altitude in Japan. *Thorax* 1996;51:739–42.
- [68] Schutte H, Lohmeyer J, Rosseau S, Ziegler S, Siebert C, Kielisch H, et al. Bronchoalveolar and systemic cytokine profiles in patients with ARDS, severe pneumonia and cardiogenic pulmonary oedema. *Eur Respir J* 1996;9:1858–67.
- [69] De Pasquale CG, Arnolda LF, Doyle IR, Grant RL, Aylward PE, Bersten AD. Prolonged alveolocapillary barrier damage after acute cardiogenic pulmonary edema. *Crit Care Med* 2003;31:1060–7.
- [70] Zimmerman GA, Crapo RO. Adult respiratory distress syndrome secondary to high altitude pulmonary edema. *High Alt Med Biol* 1980;133:335–7.
- [71] Mairbaurl H, Schwobel F, Hoschele S, Maggiorini M, Gibbs S, Swenson ER, et al. Altered ion transporter expression in bronchial epithelium in mountaineers with high-altitude pulmonary edema. *J Appl Physiol* 2003;95:1843–50.
- [72] Wodopia R, Ko HS, Billian J, Wiesner R, Bartsch P, Mairbaurl H. Hypoxia decreases proteins involved in epithelial electrolyte transport in a549 cells and rat lung. *Am J Physiol Lung Cell Mol Physiol* 2000;279:L1110–9.
- [73] Planes C, Escoubet B, Blot-Chabaud M, Friedlander G, Farnan N, Clerici C. Hypoxia downregulates expression and activity of epithelial sodium channels in rat alveolar epithelial cells. *Am J Respir Cell Mol Biol* 1997;17:508–18.
- [74] Vivona ML, Matthay M, Chabaud MB, Friedlander G, Clerici C. Hypoxia reduces alveolar epithelial sodium and fluid transport in rats: reversal by beta-adrenergic agonist treatment. *Am J Respir Cell Mol Biol* 2001;25:554–61.
- [75] Knowles MR, Carson JL, Collier AM, Gatzky JT, Boucher RC. Measurements of nasal transepithelial electric potential differences in normal human subjects in vivo. *Am Rev Respir Dis* 1981;124:484–90.
- [76] Mairbaurl H, Weymann J, Mohrlein A, Swenson ER, Maggiorini M, Gibbs JS, et al. Nasal potential difference at high altitude (4559 m): evidence for secretion. *Am J Respir Crit Care Med* 2003;9:9.
- [77] Sartori C, Duplain H, Lepori M, Egli M, Maggiorini M, Nicod P, et al. High altitude impairs nasal transepithelial sodium transport in HAPE-prone subjects. *Eur Respir J* 2004;23:916–20.
- [78] Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med* 2002;346:1631–6.
- [79] Perkins GD, McAuley DF, Thickett DR, Gao F. The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2006;173:281–7.
- [80] Groshaus HE, Manocha S, Walley KR, Russell JA. Mechanisms of beta-receptor stimulation-induced improvement of acute lung injury and pulmonary edema. *Crit Care* 2004;8:234–42.
- [81] Matthay MA, Abraham E. Beta-adrenergic agonist therapy as a potential treatment for acute lung injury. *Am J Respir Crit Care Med* 2006;173:254–5.
- [82] Adding LC, Agvald P, Artlich A, Persson MG, Gustafsson LE. Beta-adrenoceptor agonist stimulation of pulmonary nitric oxide production in the rabbit. *Br J Pharmacol* 1999;126:833–9.
- [83] Khimenko PL, Barnard JW, Moore TM, Wilson PS, Ballard ST, Taylor AE. Vascular permeability and epithelial transport effects on lung edema formation in ischemia and reperfusion. *J Appl Physiol* 1994;77:1116–21.
- [84] Parker JC, Ivey CL. Isoproterenol attenuates high vascular pressure-induced permeability increases in isolated rat lungs. *J Appl Physiol* 1997;83:1962–7.
- [85] McAuley DF, Frank JA, Fang X, Matthay MA. Clinically relevant concentrations of beta2-adrenergic agonists stimulate maximal cyclic adenosine monophosphate-dependent airspace fluid clearance and decrease pulmonary edema in experimental acid-induced lung injury. *Crit Care Med* 2004;32:1470–6.
- [86] Maris NA, de Vos AF, Dessing MC, Spek CA, Lutter R, Jansen HM, et al. Antiinflammatory effects of salmeterol after inhalation of

- lipopolysaccharide by healthy volunteers. *Am J Respir Crit Care Med* 2005;172:878–84.
- [87] Bartsch P, Roach R. Acute mountain sickness and high-altitude cerebral edema. In: Hornbein TF, Schoene RB, editors. *High altitude: an exploration of human adaptation*. New York: Marcel Dekker; 2001. p. 731–76.
- [88] Erba P, Anastasi S, Senn O, Maggiorini M, Bloch KE. Acute mountain sickness is related to nocturnal hypoxemia but not to hypoventilation. *Eur Respir J* 2004;24:303–8.
- [89] Hackett PH, Roach RC, Schoene RB, Harrison GL, Mills Jr WJ. Abnormal control of ventilation in high-altitude pulmonary edema. *J Appl Physiol* 1988;64:1268–72.
- [90] Matsuzawa Y, Fujimoto K, Kobayashi T, Namushi NR, Harada K, Kohno H, et al. Blunted hypoxic ventilatory drive in subjects susceptible to high-altitude pulmonary edema. *J Appl Physiol* 1989;66:1152–7.
- [91] Hohenhaus E, Paul A, McCullough RE, Kucherer H, Bartsch P. Ventilatory and pulmonary vascular response to hypoxia and susceptibility to high altitude pulmonary oedema. *Eur Respir J* 1995;8:1825–33.
- [92] Carpenter TC, Reeves JT, Durmowicz AG. Viral respiratory infection increases susceptibility of young rats to hypoxia-induced pulmonary edema. *J Appl Physiol* 1998;84:1048–54.
- [93] Durmowicz AG, Noordweir E, Nicholas R, Reeves JT. Inflammatory processes may predispose children to high-altitude pulmonary edema. *J Pediatr* 1997;130:838–40.
- [94] Fiorenzano G, Rastelli V, Greco V, Di Stefano A, Dottorini M. Unilateral high-altitude pulmonary edema in a subject with right pulmonary artery hypoplasia. *Respiration* 1994;61:51–4.
- [95] Hackett PH, Creagh CE, Grover RF, Honigman B, Houston CS, Reeves JT, et al. High altitude pulmonary edema in persons without the right pulmonary artery. *N Engl J Med* 1980;302:1070–3.
- [96] Hyers TM, Fowler AA, Wicks AB. Focal pulmonary edema after massive pulmonary embolism. *Am Rev Respir Dis* 1981;123:232–3.
- [97] Nakagawa S, Kubo K, Koizumi T, Kobayashi T, Sekiguchi M. High-altitude pulmonary edema with pulmonary thromboembolism. *Chest* 1993;103:948–50.
- [98] Viswanathan R, Jain SK, Subramanian S, Subramanian TAV, Dua GL, Giri J. Pulmonary edema of high altitude: II. Clinical, aerodynamic and biochemical studies in a group with history of pulmonary edema of high altitude. *Am Rev Respir Dis* 1969;100:334–49.
- [99] Durmowicz AG. Pulmonary edema in 6 children with Down syndrome during travel to moderate altitudes. *Pediatrics* 2001;108:443–7.
- [100] Naeije R, De Backer D, Vachiery JL, De Vuyst P. High-altitude pulmonary edema with primary pulmonary hypertension. *Chest* 1996;110:286–9.
- [101] Levine BD, Grayburn PA, Voyles WF, Greene ER, Roach RC, Hackett PH. Intracardiac shunting across a patent foramen ovale may exacerbate hypoxemia in high-altitude pulmonary edema. *Ann Intern Med* 1991;114:569–70.
- [102] Eldridge MW, Braun RK, Yoneda KY, Walby WF. Effects of altitude and exercise on pulmonary capillary integrity: evidence for subclinical high-altitude pulmonary edema. *J Appl Physiol* 2006;100:972–80.
- [103] Naeije R, Mélot C, Niset G, Delcroix M, Wagner PD. Improved arterial oxygenation by a pharmacological increase in chemosensitivity during hypoxic exercise in normal subjects. *J Appl Physiol* 1993;78:1666–71.
- [104] Reeves JT, Dempsey JA, Grover RF. Pulmonary circulation during exercise. In: Weir EK, Reeves JT, editors. *Pulmonary vascular physiology and pathophysiology*. New York: Marcel Dekker; 1989. p. 107–33.
- [105] Eldridge MW, Podolsky A, Richardson RS, Johnson DH, Knight RD, Johnson EC, et al. Pulmonary hemodynamic response to exercise in subjects with prior high-altitude pulmonary edema. *J Appl Physiol* 1996;81:911–21.
- [106] Ritter M, Jenni R, Maggiorini M, Grimm J, Oelz O. Abnormal left ventricular diastolic filling patterns in acute hypoxic pulmonary hypertension at high altitude. *Am J Noninvasive Cardiol* 1993;7:33–8.
- [107] Bartsch P, Mairbaur H, Swenson ER, Maggiorini M. High altitude pulmonary oedema. *Swiss Med Wkly* 2003;133:377–84.
- [108] Ghofrani HA, Reichenberger F, Kohstall MG, Mrosek EH, Seeger T, Olschewski H, et al. 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* 2004;141:169–77.
- [109] Greene MK, Kerr AM, McIntosh IB, Prescott RJ. Acetazolamide in prevention of acute mountain sickness: a double-blind controlled cross-over study. *Br Med J (Clin Res Ed)* 1981;283:811–3.
- [110] Basnyat B, Gertsch JH, Johnson EW, Castro-Marin F, Inoue Y, Yeh C. Efficacy of low-dose acetazolamide (125 mg bid) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. *High Alt Med Biol* 2003;4:45–52.
- [111] Hohne C, Krebs MO, Seiferheld M, Boemke W, Kaczmarczyk G, Swenson ER. Acetazolamide prevents hypoxic pulmonary vasoconstriction in conscious dogs. *J Appl Physiol* 2004;97:515–21.
- [112] Berg JT, Ramanathan S, Swenson ER. Inhibitors of hypoxic pulmonary vasoconstriction prevent high-altitude pulmonary edema in rats. *Wilderness Environ Med* 2004;15:32–7.
- [113] Rock PB, Johnson TS, Larsen RF, Fulco CS, Trad LA, Cymerman A. Dexamethasone as prophylaxis for acute mountain sickness. Effect of dose level. *Chest* 1989;95:568–73.
- [114] Ellsworth AJ, Larson EB, Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med* 1987;83:1024–30.
- [115] Murata T, Hori M, Sakamoto K, Karaki H, Ozaki H. Dexamethasone blocks hypoxia-induced endothelial dysfunction in organ-cultured pulmonary arteries. *Am J Respir Crit Care Med* 2004;170:647–55.
- [116] Asoh K, Kumai T, Murano K, Kobayashi S, Koitabashi Y. Effect of antenatal dexamethasone treatment on Ca²⁺-dependent nitric oxide synthase activity in rat lung. *Pediatr Res* 2000;48:91–5.
- [117] Scherrer U, Vollenweider P, Randin D, Jequier E, Nicod P, Tappy L. Suppression of insulin-induced sympathetic activation and vasodilation by dexamethasone in humans. *Circulation* 1993;88:388–94.
- [118] Matthay MA, Clerici C, Saumon G. Invited review: active fluid clearance from the distal air spaces of the lung. *J Appl Physiol* 2002;93:1533–41.
- [119] Stelzner TJ, O'Brien RF, Sato K, Weil JV. Hypoxia-induced increases in pulmonary transvascular protein escape in rats. Modulation by glucocorticoids. *J Clin Invest* 1988;82:1840–7.
- [120] Stenmark KR, Davie NJ, Reeves JT, Frid MG. Hypoxia, leukocytes, and the pulmonary circulation. *J Appl Physiol* 2005;98:715–21.
- [121] Wang JY, Yeh TF, Lin YC, Miyamura K, Holmskov U, Reid KB. Measurement of pulmonary status and surfactant protein levels during dexamethasone treatment of neonatal respiratory distress syndrome. *Thorax* 1996;51:907–13.
- [122] Young SL, Silbajoris R. Dexamethasone increases adult rat lung surfactant lipids. *J Appl Physiol* 1986;60:1665–72.
- [123] King JS, Greenlee RR. Successful use of the Gamow hyperbaric bag in the treatment of altitude illness at Mount Everest. *J Wilderness Med* 1990;1:193–202.
- [124] Taber RL. Protocols for the use of portable hyperbaric chamber for the treatment of high altitude disorders. *J Wilderness Med* 1990;1:181–92.
- [125] Hultgren HN, Honigman B, Theis K, Nicholas D. High-altitude pulmonary edema at a ski resort. *High Alt Med Biol* 1996;164:222–7.
- [126] Schoene RB, Roach RC, Hackett PH, Harrison G, Mills Jr WJ. High altitude pulmonary edema and exercise at 4400 meters on Mount McKinley. Effect of expiratory positive airway pressure. *Chest* 1985;87:330–3.
- [127] Larson EB. Positive airway pressure for high-altitude pulmonary oedema. *Lancet* 1985;1:371–3.
- [128] Oelz O. High altitude cerebral oedema after positive airway pressure breathing at high altitude. *Lancet* 1983;2:1148.