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Review

High altitude-induced pulmonary oedema

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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.

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

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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) PO_2, PCO_2, and the alveolar–arterial difference for oxygen ($AaDO_2$) 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 PO_2 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].

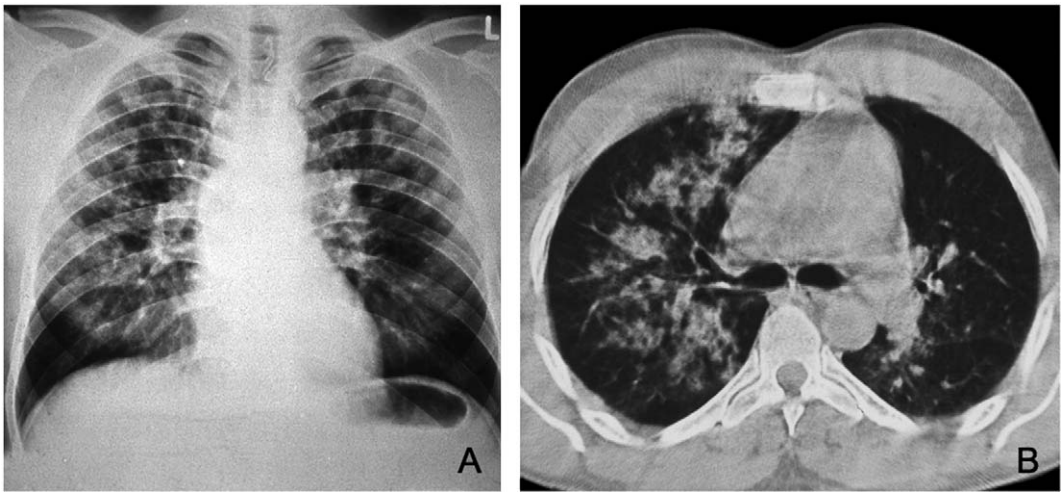

Fig. 1. Chest radiograph and CT-scan in a mountaineer with HAPE. Radiograph of a male patient with HAPE showing patchy distributed infiltrates over the whole lung (A). The CT-thorax of the same patient shows a patchy distribution of oedema, localized predominately around the right hilus (B). (These illustrations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

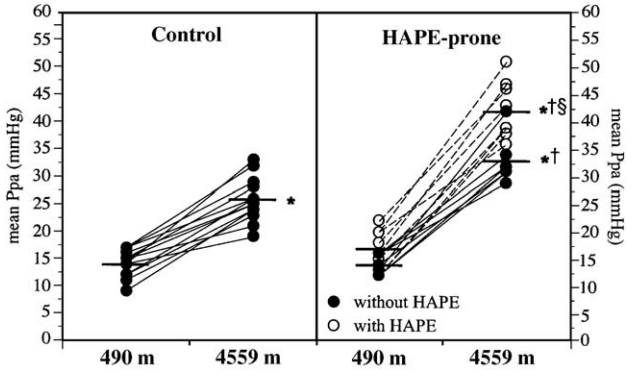

Fig. 2. Changes in mean pulmonary artery pressure from low to high altitude. Individual mean pulmonary artery pressures (Ppa) measured at 4559 m in HAPE-resistant (control) and HAPE-prone (susceptible) adults [30]. The closed dots indicate mean Ppa in individuals without radiographic evidence of HAPE. 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.

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 μm 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].

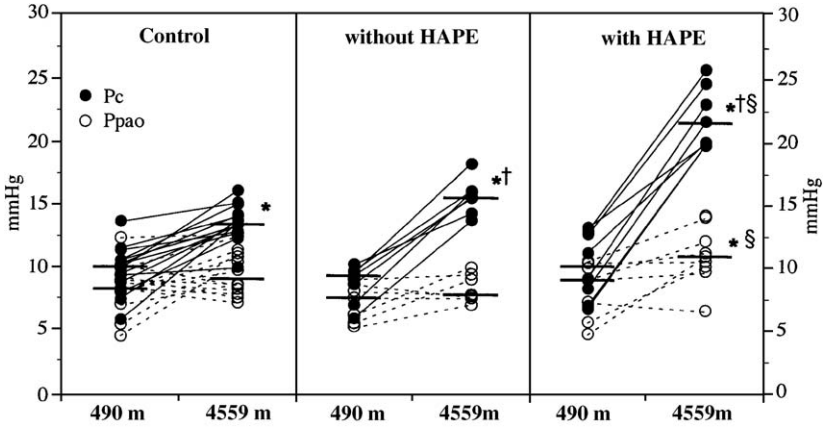

Fig. 3. Changes in pulmonary capillary pressure and pulmonary artery occlusion pressure upon ascent to 4559 m. Individual pulmonary capillary pressure (Pc) and pulmonary artery occluded pressure (Ppao = wedge pressure), assessed using the arterial occlusion technique, in controls, and HAPE-susceptible 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,

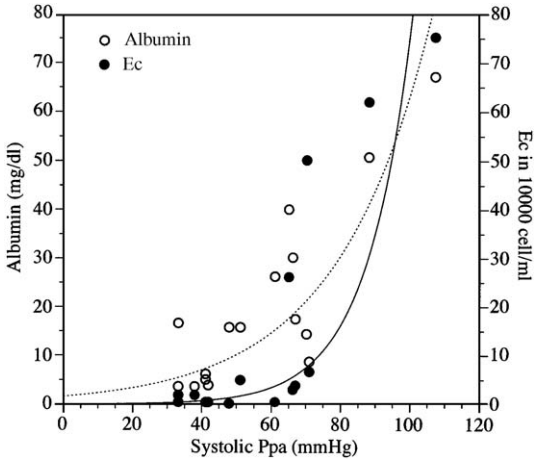

Fig. 4. Relationship between systolic pulmonary artery pressure and BAL red blood cell count and albumin concentration. Individual broncho-alveolar lavage (BAL) red blood cell and albumin concentration plotted against systolic pulmonary artery pressure (sPpa) at high altitude (4559 m). The figure shows 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].

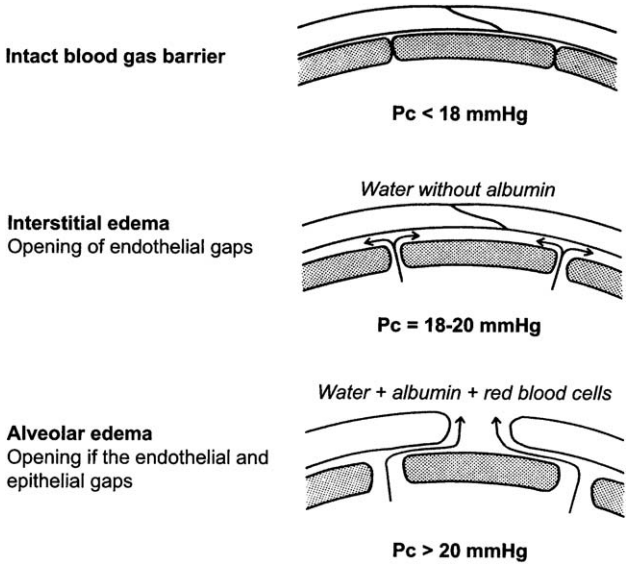

Fig. 5. Mechanism of pulmonary capillary leak in HAPE. Elevated pulmonary capillary pressure (Pc) cause progressive distension of the vessel wall leading to opening of endothelial and epithelial gaps through which first proteins and later red blood cells leak into the alveolar space.

IL-8, thromboxane, prostaglandin E_2, and leukotriene B_4 (LTB_4), 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 LTB_4 [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.

β_2-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 β_2-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, β_2-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]

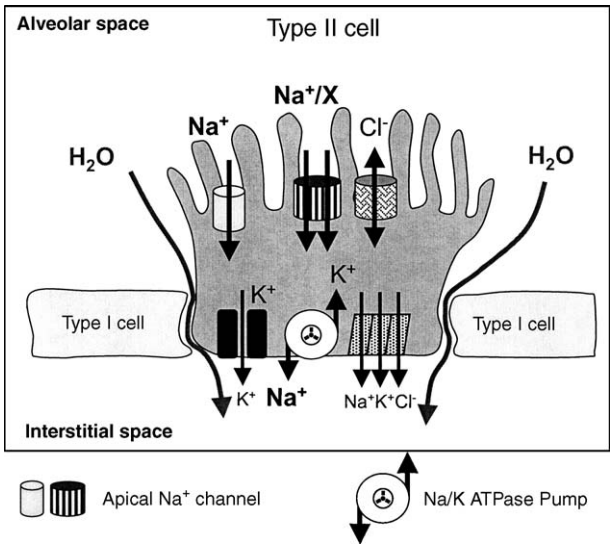

Fig. 6. Alveolar epithelial cell fluid reabsorbing mechanism. Alveolar epithelial apical and basolateral membrane ion channels and exchangers involved in active transepithelial sodium and water absorption. There is an active reabsorption of sodium; water and chloride follow passively. Acute hypoxia reduces 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 PaO_2 (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.

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