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Acclimatisation at high altitude: lessons from individuals prone to high altitude pulmonary oedema

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ABSTRACT High altitude constitutes an exciting natural laboratory for medical research. Over the past decade, the scope of high altitude research has broadened considerably, since it has become clear that the results of this research may have important implications, not only for the understanding of diseases in the millions of people living permanently at high altitude, but also for the treatment of hypoxemia-related disease states in patients living at low altitude. Studies in subgroups of subjects who do not adapt well to high altitude have greatly advanced our knowledge regarding underlying mechanisms predisposing to these diseases. high altitude pulmonary oedema is the best studied example of such a maladaptation. Here we will review recent work of our group that has provided novel insight in the pathogenesis of HAPE.

KEYWORDS Altitude, alveolar fluid clearance, endothelial dysfunction, hypoxia, pulmonary hypertension, pulmonary oedema.

LIST OF ABBREVIATIONS Acute mountain sickness (AMS), Endothelin-1 (ET-1), high altitude pulmonary oedema (HAPE), epithelial sodium channel (ENaC), nitric oxide (NO), pulmonary artery pressure (PAP)

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INTRODUCTION

Due to its critical role in energy production, oxygen is essential for cell survival. A reduction in tissue oxygen availability stimulates a complex series of adjustments, both at the cellular and at the systemic level. As adaptation to hypoxia proceeds, these responses are generally limited by inhibitory feedback mechanisms. There exist, however, situations in which, for unknown reasons, these feedback mechanisms are impaired, leading to exaggerated compensatory responses to hypoxia with detrimental consequences for the organism. The underlying mechanisms regulating the delicate balance between positive (self-limited) and negative (exaggerated) adjustments to hypoxia are incompletely understood.

High altitude constitutes an exciting natural laboratory for medical research. Over the past decade, the scope of high altitude research has broadened considerably, since it has become clear that the results of this research may help to fill our gaps in the knowledge of tissue adaptation to hypoxia, and, in turn, may have important implications not only for the understanding of diseases in the millions of people living permanently at high altitude, but also for the treatment of hypoxemia-related disease states in patients living at low altitude. Studies in subgroups of subjects who do not adapt well to high altitude have greatly advanced our knowledge regarding underlying mechanisms predisposing to these diseases. High altitude pulmonary oedema is the best studied example of such a maladaptation.

High altitude pulmonary oedema is a life-threatening condition occurring in predisposed, but otherwise healthy, subjects. It thereby allows the study of underlying mechanisms of pulmonary oedema in the absence of confounding factors such as coexisting cardiovascular or pulmonary disease, and drug therapy. Furthermore, the observation that there exist HAPE-resistant and HAPE-prone subjects suggests the possibility of a genetic and/or acquired predisposition.[1]

It is well established that exaggerated hypoxic pulmonary vasoconstriction is a hallmark of HAPE (see Figure 1). Pulmonary vasoconstriction is heterogeneous, and, by leading to capillary leakage either by overperfusion[2] or stress failure,[3] plays an important part in alveolar fluid flooding at high altitude.[4] However, the mechanism(s) underlying the exaggerated hypoxic pulmonary vasoconstriction in HAPE-prone subjects is still unknown.

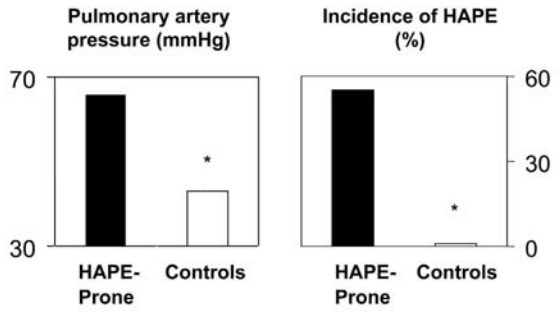

FIGURE 1 Pulmonary artery pressure and incidence of HAPE in HAPE-prone and HAPE-resistant control subjects after a rapid ascent to 4,559 m. * P<0·01 vs HAPE-prone subjects.

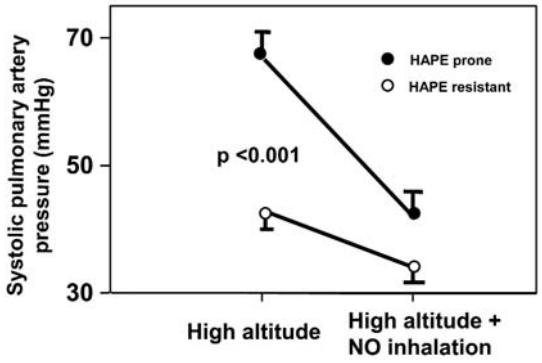

FIGURE 2 Effects of NO inhalation (40 ppm for 20 min) at high altitude (4,559 m) on systolic pulmonary artery pressure in 17 HAPE-resistant and 18 HAPE-prone subjects. * P<0·001 vs HAPE-prone subjects. (Adapted from Scherrer *et al.*[7])

MECHANISMS OF EXAGGERATED PULMONARY VASOCONSTRICTOR RESPONSIVENESS TO HIGH ALTITUDE EXPOSURE IN HAPE-SUSCEPTIBLE SUBJECTS

a. Role of impaired endothelial and epithelial NO synthesis

Endothelial NO synthesis plays an important role in the regulation of pulmonary vascular tone in humans, because inhibition of NO synthesis by L-NMMA infusion has been shown to potentiate the pulmonary vasoconstrictor response evoked by short-term hypoxic breathing.[5] When administered by inhalation, NO attenuates the pulmonary vasoconstriction evoked by short-term hypoxia.[6] In a recent study, we examined effects of NO inhalation on pulmonary artery pressure in a group of HAPE-prone mountaineers, and in a group of subjects resistant to this condition.[7] As expected, HAPE-prone subjects had more pronounced pulmonary vasoconstriction than those resistant to such oedema. During NO inhalation, however, the pulmonary artery pressure was similar in both groups, because the NO-induced decrease in pulmonary artery pressure was much larger in HAPE-prone subjects (see Figure 2). This observation suggests that defective pulmonary endothelial NO synthesis is one of the mechanisms contributing to exaggerated hypoxic pulmonary hypertension in humans. Consistent with these data, in certain populations, HAPE susceptibility has been found to be associated with eNOS polymorphisms and impaired vascular NO synthesis.[8,9]

In the respiratory system, NO is not only produced by the pulmonary vascular endothelium, but also by the respiratory epithelium, and there is evidence that the latter also regulates pulmonary artery pressure.[10] Respiratory epithelial, but not pulmonary vascular endothelial, NO synthesis can be assessed by measuring NO in the exhaled air.[11] In HAPE-prone subjects, exhaled NO at high altitude is lower than in control subjects, and there exists an inverse relationship between pulmonary artery pressure and exhaled NO at high altitude (see Figure 3).[12]

It is interesting to note here that at physiological concentrations, NO attenuates oxidative stress,[13] a condition that has been implicated in the pathogenesis of hypoxic pulmonary hypertension.[14,15] In eNOS deficient states, loss of NO inhibition of oxidative stress may therefore represent an additional mechanism facilitating pulmonary hypertension.

Taken together, these findings indicate that defective pulmonary endothelial and respiratory epithelial NO synthesis contributes to exaggerated pulmonary hypertension during short-term high altitude exposure.

b. Role of exaggerated endothelin-1 synthesis

In addition to relaxing factors, the pulmonary endothelium also synthesises vasoconstrictor factors. Endothelin-1 is the most potent among them, and plays a role in the regulation of pulmonary vascular tone during hypoxic stress.[16] High altitude exposure augments ET-1 plasma concentration in healthy subjects.[17] To examine whether ET-1 may contribute to exaggerated pulmonary vasoconstriction in HAPE-prone subjects, in a recent study, we measured ET-1 plasma levels and pulmonary artery pressure at low (580 m) and high altitude (4,559 m), in HAPE-prone and HAPE-resistant mountaineers.[18] We found that, at high altitude, ET-1 plasma levels were significantly higher in mountaineers prone to pulmonary oedema than in those resistant to oedema. Moreover, there was a direct relationship between the changes, from low to high altitude, in ET-1 plasma levels and systolic pulmonary artery pressure, and, between ET-1 plasma levels and pulmonary artery pressure measured at high altitude (see Figure 4).

These findings are consistent with the hypothesis that an augmented release of the potent pulmonary vasoconstrictor peptide ET-1, and/or its reduced

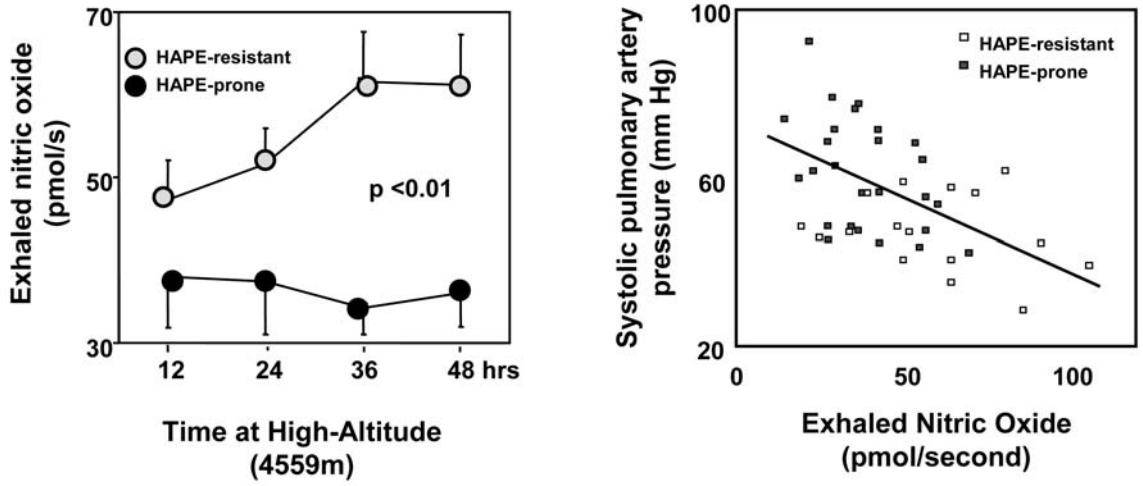

FIGURE 3 Time course of exhaled NO in HAPE-prone and -resistant subjects (left hand panel) and relationship between exhaled NO and systolic pulmonary artery pressure (right hand panel) at high altitude. (r= -0·51, p<0·001) (Adapted from Duplain *et al.*[12])

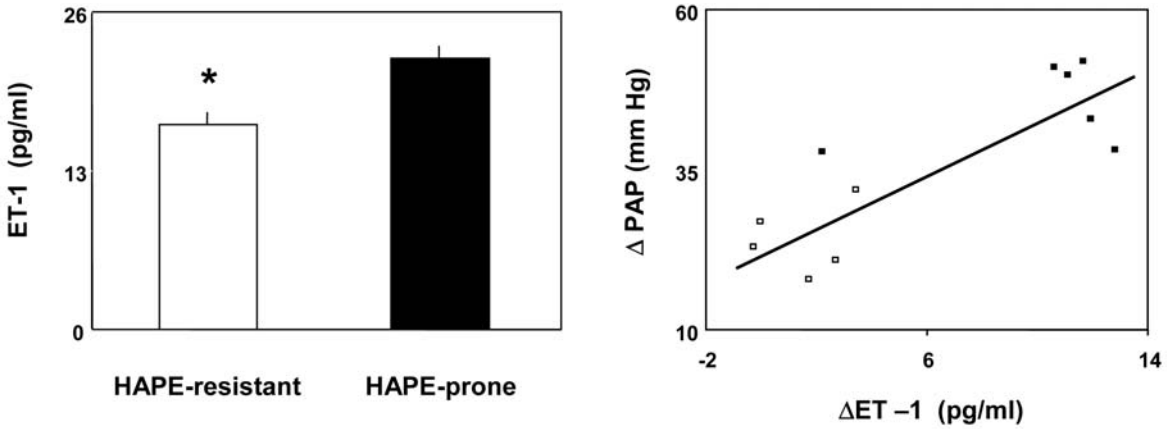

FIGURE 4 Endothelin-1 plasma concentration at high altitude (4,559 m) (left hand panel), and correlation between altitude-induced changes in systolic PAP and ET-1 plasma concentration (right hand panel) in HAPE-prone and HAPE-resistant subjects. * P<0·05 patients vs control subjects. (r= 0·83, p<0·01) (Adapted from Sartori *et al.*[39])

pulmonary clearance, could represent an additional mechanism contributing to exaggerated pulmonary hypertension at high altitude. Finally, and most interestingly, in human endothelial cells, NO inhibits the hypoxia-induced stimulation of ET-1 gene expression and synthesis,[19 20] suggesting that the defect in NO-synthesis and augmented ET-1 synthesis could be causally related.

c. Role of the sympathetic nerve overactivity

Cardiovascular adjustments to hypoxia are mediated, at least in part, by the sympathetic nervous system, and sympathetic activation promotes pulmonary vasoconstriction and alveolar fluid flooding in experimental animals.[21] Thus, it appears possible that the sympathetic nervous system may contribute to exaggerated pulmonary hypertension in HAPE-susceptible subjects. To test this hypothesis, we measured, in HAPE-prone and -resistant mountaineers, sympathetic nerve activity (using intraneural microelectrodes) targeted at the skeletal vasculature, and pulmonary artery pressure during high altitude exposure.[22] We found that, in subjects prone to pulmonary oedema, the sympathetic firing rate was markedly augmented, and that the sympathetic overactivation preceded the development of lung oedema. We also observed a direct relationship between sympathetic nerve activity and pulmonary artery pressure at high altitude.

These data provide the first evidence for an exaggerated sympathetic activation in HAPE-prone subjects during actual high altitude exposure. They suggest that sympathetic overactivation may contribute to high altitude induced exaggerated pulmonary hypertension in HAPE-susceptible subjects. Consistent with this hypothesis, in subjects suffering from HAPE, infusion of the alpha-adrenergic blocking agent phentolamine evokes markedly larger decreases in pulmonary artery pressure than other, non-specific vasodilators.[23] Finally, there is evidence both in experimental animals and in humans that NO buffers sympathetic nerve outflow. It therefore appears possible that in HAPE-prone subjects defective

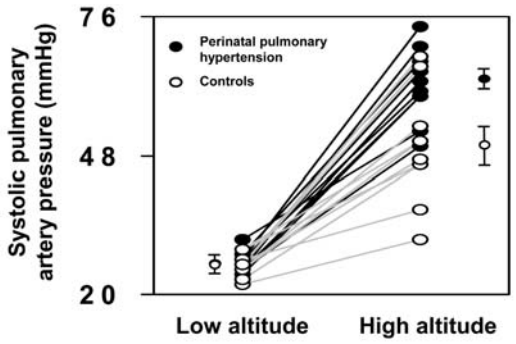

FIGURE 5 Effects of high altitude exposure (4,559 m) on systolic pulmonary artery pressure in ten healthy young adults with a history of transient perinatal pulmonary hypertension (filled circles) and in ten control subjects (open circles). * P<0·01 patients vs control subjects. (Adapted from Sartori *et al.*[26])

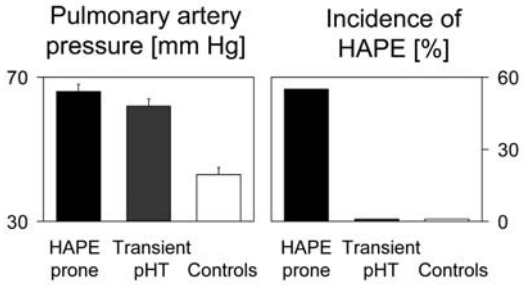

FIGURE 6 Effects of high altitude exposure (4,559 m) on pulmonary artery pressure and incidence of HAPE in 18 HAPE-prone subjects, 10 healthy young adults with a history of transient perinatal pulmonary hypertension, and 17 HAPE-resistant control subjects. (Adapted from Sartori *et al.*[28])

NO synthesis may contribute to exaggerated altitude-induced sympathetic activation.

In summary, HAPE-prone subjects are characterised by exaggerated pulmonary hypertension which may be related to pulmonary endothelial and epithelial dysfunction and sympathetic overactivation. Defective NO synthesis/decreased NO bioavailability may represent a central underlying mechanism in the pathogenesis of this exaggerated hypoxic pulmonary hypertension.

While these observations demonstrate the key role of NO in the pathogenesis of HAPE, the factors predisposing individuals to pulmonary vasoconstriction are not known.

d. Role of perinatal vascular imprint

Epidemiological studies suggest that adverse events *in utero* are associated with cardiovascular and metabolic disease in adulthood.[24] During the perinatal period, the pulmonary circulation undergoes important structural and functional changes to allow the sudden transition from gas exchange by the placenta to gas exchange by the lungs. These changes allow a dramatic, roughly ten-fold, increase in pulmonary blood flow and a corresponding decrease in pulmonary vascular resistance. During the perinatal period the pulmonary circulation is particularly vulnerable to noxious stimuli such as hypoxia. Studies in rats have suggested that transitory exposure to hypoxia during the first few days of life, which induces transient pulmonary hypertension, predisposes to augmented pulmonary vasoconstrictor responses to hypoxia in adult life.[25]

To test for the existence of such a predisposition in man, we measured pulmonary vasoconstrictor responses to high altitude exposure in a group of young healthy adults who had suffered from transient hypoxic pulmonary hypertension during their perinatal period, and compared these responses with those observed in young adults who had not suffered from any complication during the perinatal period.[26] We found that in young adults who had suffered from transient perinatal pulmonary hypertension, the altitude-induced increase in pulmonary artery pressure was more than 50% larger than in control subjects (see Figure 5). This augmented pulmonary vasoconstrictor response could not be attributed to more severe oxygen desaturation in the circulating blood, because the degree of the altitude-induced hypoxaemia was comparable in both groups. The underlying mechanism causing the exaggerated pulmonary vasoconstrictor responsiveness is not known. Experimental data in rats exposed to transitory hypoxia during their first few days of life, suggest that the augmented hypoxia-induced pulmonary vasoconstriction later in life may be related to impaired NO synthesis in the lungs.[27]

3. Exaggerated pulmonary hypertension per se, is not sufficient to trigger HAPE

The exaggerated pulmonary vasoconstriction in these young adults was of similar magnitude as the one observed previously in HAPE-prone mountaineers studied under the same conditions. Surprisingly, however, none of the subjects had clinical, radiographic, or laboratory (widening of the alveolar arterial oxygen difference) evidence of alveolar fluid flooding.[28] This finding contrasts with the roughly 70% incidence of pulmonary oedema which has consistently been found in HAPE-prone subjects studied under the same conditions (see Figure 6). This very important observation suggests that exaggerated pulmonary hypertension *per se* may not always be sufficient to trigger HAPE, and that additional mechanisms play a role. A defect in transepithelial alveolar sodium transport may represent such a candidate mechanism.

4. Does a defect of the alveolar transepithelial sodium transport act as a sensitiser to pulmonary oedema?

Pulmonary oedema results from an imbalance between the leak of fluid into the airspace, and its removal.[29] While

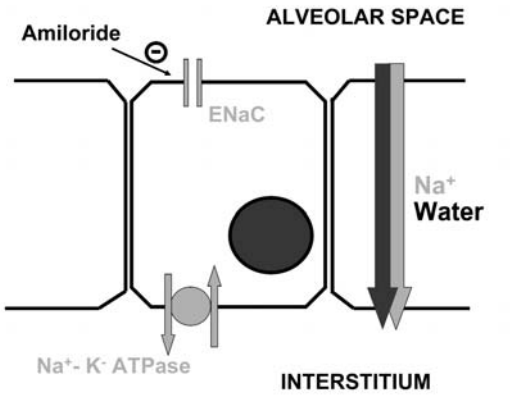

FIGURE 7 Mechanisms involved in the alveolar transepithelial sodium (and water) transport. Sodium is taken up by the alveolar cell at the apical surface, primarily through the amiloride-sensitive sodium channel (ENaC). Once taken up, the sodium is then pumped out of the cell into the lung interstitium by the Na-K-ATPase located at the basolateral membrane. Water follows passively along this osmotic gradient.

for many years, it was believed that Starling forces and lymphatic drainage entirely account for the removal of excess intra-alveolar fluid, it is now clear that both active and facilitated transepithelial sodium transport play an important part. Sodium is taken up by the alveolar cells at the apical surface, primarily through the amiloride-sensitive sodium channel (ENaC). Once taken up, the sodium is then pumped out of the cell into the lung interstitium by the Na-K-ATPase located at the basolateral membrane. Water follows passively across this osmotic gradient (see Figure 7).[30]

ENaC is thought to be the limiting step of transepithelial sodium transport. In isolated animal lungs, in *ex vivo* resected human lungs, and in intact animals, the amiloride-sensitive sodium transport accounts for approximately 40–60% of the alveolar fluid clearance. The key role of this transport, in removing the fluid from the airspace, has been demonstrated by transgenic mice lacking the a-subunit of the ENaC which develop respiratory distress and die shortly after birth from failure to clear their lungs of liquid.[31] Clinically more relevant, we recently provided the first evidence *in vivo* that a subclinical impairment of the respiratory sodium transport acts as a sensitiser to lung oedema, because it facilitates pulmonary water accumulation and delays its clearance from the airspaces.[32]

We wondered whether a similar mechanism could be operational *in humans,* and if so, may contribute to HAPE susceptibility. We, therefore, measured, at low altitude, nasal potential difference (a reliable marker of the sodium transport across the respiratory epithelium of the lower respiratory tract)[33], in HAPE-prone and HAPE-resistant mountaineers. To assess specifically the contribution of the ENaC, we also measured the effects of amiloride superfusion on the nasal potential difference.[34] We found that HAPE-prone subjects had

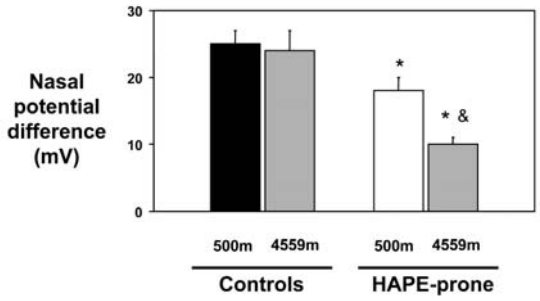

FIGURE 8 Nasal potential difference (a reliable marker of alveolar fluid clearance) at low and high altitude in HAPE-prone and HAPE-resistant subjects. * P< 0·05 vs corresponding values in control subjects; and P<0·05 vs corresponding values at low altitude. (Adapted from Sartori *et al.*[35])

decreased nasal potential difference. This impairment appeared to be related, at least in part, to a defect in ENaC function, because amiloride superfusion induced a significantly smaller decrease in the nasal potential difference in HAPE-prone than in HAPE-resistant subjects. Subsequently, and consistent with data *in vitro*, we showed that high altitude exposure further impairs this transport in HAPE-prone, but not in control subjects (see Figure 8).[35] Finally, and more importantly, we showed that prophylactic stimulation of respiratory sodium transport by the inhalation of the beta-adrenergic agonist salmeterol decreased the incidence of high altitude pulmonary oedema in susceptible subjects by more than 50%.[34] These findings support the concept that the combination of a constitutive and an acquired defect in sodium-driven alveolar fluid clearance facilitates the development of pulmonary oedema in humans, and that this transport represents an appropriate target for therapy.

CONCLUSION

Based on our results, we suggest the following new concept for the pathogenesis of HAPE (see Figure 9):

Pulmonary oedema results from a persistent imbalance between the forces that drive water into the airspace and the biologic mechanisms for its removal. In HAPE-prone subjects, alveolar fluid flooding results from an augmented capillary shear stress. This latter is due to exaggerated heterogeneous hypoxic pulmonary vasoconstriction which appears to be related, at least in part, to endothelial dysfunction, sympathetic overactivation, and/or perinatal insults. Defective pulmonary NO synthesis/bioavailability may represent the common underlying mechanisms linking these defects.

Exaggerated pulmonary hypertension *per se*, however, is not sufficient to trigger HAPE, as evidenced by studies in young adults with transient perinatal pulmonary hypertension, and additional mechanisms appear to play a role. Our findings suggest that HAPE-prone subjects are

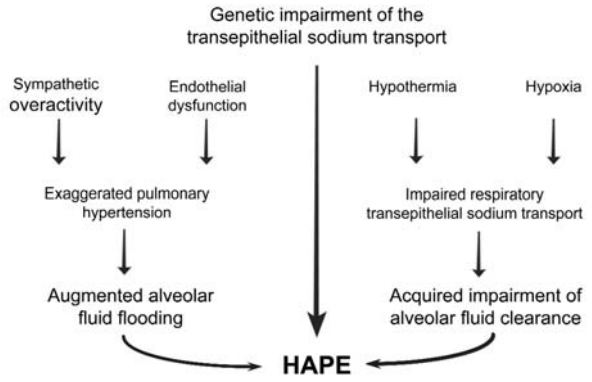

FIGURE 9 Mechanisms involved in the pathogenesis of HAPE.

characterised by a, possibly genetic, defect of the transepithelial sodium (and water) transport. High altitude exposure (due to hypoxia[36, 37] and/or hypothermia[38]) further impairs this transport. The conjunction of these pulmonary vascular endothelial and alveolar epithelial defects ultimately leads to high altitude pulmonary oedema.

TREATMENT OF HAPE

HAPE is a life-threatening condition best managed by descent. Other treatment options should never be considered as a substitute for rapid descent, but should be used either to improve the clinical condition to facilitate descent, or to gain time, when descent is impossible because of bad weather conditions or objective dangers such as avalanches. In this latter situation, and if available, oxygen at a rate of 2–4 l/min should be administered to improve arterial oxygenation and decrease pulmonary artery pressure. Since both oxygen administration and descent (pressurisation) are effective, during high altitude expeditions, portable hyperbaric chambers (Gamow [USA], Certec [France]) which are lighter to carry than oxygen cylinders, are of interest. Using these devices, treatment is sustainable for hours (the continuous pumping necessary to maintain pressurisation and evacuate carbon dioxide can be tiring, however). Moreover, it is possible to administer supplemental oxygen inside the bag in the case of severe illness. There may be a rebound effect on stopping hyperbaria.

Several vasodilator agents (nifedipine, hydralazine, phentolamine, nitric oxide) have been used successfully to treat HAPE under experimental conditions. Among them, nifedipine which can be administered orally, has proven to be effective and relatively well tolerated. In one study, subjects given slow release nifedipine (20 mg every eight hours) without supplemental oxygen, improved arterial oxygenation and symptoms, cleared radiographic oedema, while continuing to stay at the same altitude (4,559 m).

PREVENTION OF HAPE

Some recommendations, aimed chiefly to avoid AMS, can also be formulated to reduce the risk of HAPE (see Figure 9):

1. Take sufficient time to acclimatise at an intermediate altitude of 2,500 meters (staging), and avoid raising the sleeping altitude by more than 400 meters per day thereafter.
2. Drink plenty of fluid during the stay and limit the salt intake.
3. A high carbohydrate diet increases the respiratory quotient and may improve oxygen utilisation.
4. Avoid alcohol and hypnotic drugs that may impair the hypoxic ventilatory response.
5. When arriving at high altitude, avoid unnecessary exertion because it potentiates the pulmonary vasoconstriction.
6. In mountaineers who have suffered from HAPE before, sustained release nifedipine started on the day before ascent and continued during the first three to five days after ascent may be used. Potential adverse effects during short-term use, unknown long-term efficacy and possible rebound effects on withdrawal, however, limit the routine administration of this drug for HAPE prophylaxis.
7. Prophylactic beta-2-adrenergic agonist salmeterol started on the day before ascent and continued during the stay at high altitude, has been shown to be beneficial in subjects at high risk of HAPE possibly because it stimulates the respiratory transepithelial sodium transport, and, in turn, alveolar fluid clearance.

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REFERENCES

1 Sartori C, Trueb L, Scherrer U. High-altitude pulmonary edema. Mechanisms and management. *Cardiologia* 1997; **42(6):**559–67.
2 Hultgren HN. High-altitude pulmonary edema: current concepts. *Ann Rev Med* 1996; **47:**267–84.
3 West JB, Mathieu-Costello O. High altitude pulmonary edema is caused by stress failure of pulmonary capillaries. *Int J Sports Med* 1992; **13:**S54–S8.
4 Hultgren H. *High altitude pulmonary edema.* In: Staub N (editor). Water and Solute Exchanges. New York, NY: Marcel Dekker; 1978;437–64.
5 Blitzer ML, Loh E, Roddy MA, Stamler JS, Creager MA. Endothelium-derived nitric oxide regulates systemic and pulmonary vascular resistance during acute hypoxia in humans. *J Am Coll Cardiol* 1996; **28(3):**591–6.
6 Frostell CG, Fratacci M-D, Wain JC, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991; **83:**2038–47.
7 Scherrer U, Vollenweider L, Delabays A *et al.* Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 1996; **334:**624–9.
8 Ahsan A, Charu R, Pasha MA *et al.* eNOS allelic variants at the same locus associate with HAPE and adaptation. *Thorax* 2004; **59(11):**1000–2.
9 Droma Y, Hanaoka M, Ota M *et al.* Positive association of the endothelial nitric oxide synthase gene polymorphisms with high-altitude pulmonary edema. *Circulation* 2002; **106(7):**826–30.
10 Settergren G, Angdin M, Astudillo R *et al.* Decreased pulmonary vascular resistance during nasal breathing: modulation by endogenous nitric oxide from the paranasal sinuses. *Acta Physiol Scand* 1998; **163(3):**235–9.
11 Sartori C, Lepori M, Busch T *et al.* Exhaled nitric oxide does not provide a marker of vascular endothelial function in healthy humans. *Am J Respir Crit Care Med* 1999; **160(3):**879–82.
12 Duplain H, Sartori C, Lepori M *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(1):**221–4.
13 Mohanakumar KP, Thomas B, Sharma SM, Muralikrishnan D, Chowdhury R, Chiueh CC. Nitric oxide: an antioxidant and neuroprotector. *Ann N Y Acad Sci* 2002; **962:**389–401.
14 Hoshikawa Y, Ono S, Suzuki S *et al.* Generation of oxidative stress contributes to the development of pulmonary hypertension induced by hypoxia. *J Appl Physiol* 2001; **90(4):**1299–306.
15 Bowers R, Cool C, Murphy RC *et al.* Oxidative stress in severe pulmonary hypertension. *Am J Respir Crit Care Med* 2004; **169(6):**764–9.
16 Yanagisawa M, Kurihara H, Kimura S *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988; **332:**411–5.
17 Goerre S, Wenk M, Bärtsch P *et al.* Endothelin-1 in pulmonary hypertension associated with high altitude exposure. *Circulation* 1995; **91:**359–64.
18 Sartori C, Vollenweider L, Löffler B-M *et al.* Exaggerated endothelin release in high-altitude pulmonary edema. *Circulation* 1999; **99:**2665–8.
19 Kourembanas S, McQuillan LP, Leung GK, Faller DV. Nitric oxide regulates the expression of vasoconstrictors and growth factors by vascular endothelium under both normoxia and hypoxia. *J Clin Invest* 1993; **92:**99–104.
20 Faller DV. Endothelial cell responses to hypoxic stress. *Clin Exp Pharmacol Physiol* 1999; **26(1):**74–84.
21 Krasney JA. A neurogenic basis for acute altitude illness. *Med Sci Sports Exerc* 1994; **26(2):**195–208.
22 Duplain H, Vollenweider L, Delabays A, Nicod P, Bärtsch 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.
23 Hackett PH, Roach RC, Hartig GS, Green ER, Levine BD. The effect of vasodilatators on pulmonary hemodynamics in high-altitude pulmonary edema – a comparison. *Int J Sports Med* 1992; **13:**68–74.
24 Barker DJP. *Mothers, babies, and disease in later life.* London: BMJ Books; 1994.
25 Hakim TS, Mortola JP. Pulmonary vascular resistance in adult rats exposed to hypoxia in the neonatal period. *Can J Physiol Pharmacol* 1990; **68:**419–24.
26 Sartori C, Allemann Y, Trueb L, Delabays A, Nicod P, Scherrer U. Augmented vasoreactivity in adult life associated with perinatal vascular insult. *Lancet* 1999; **353:**2205–7.
27 Smith APL, Emery CJ, Higenbottam TW. Perinatal chronic hypoxia decreases endothelial nitric oxide synthase (NOS III) and increases preproendothelin-1 (ppET-1) mRNA levels in rat. *Eur Respir J* 1997; **10(Suppl 25):**433s (Abstract).
28 Sartori C, Allemann Y, Trueb L *et al.* Exaggerated pulmonary hypertension is not sufficient to trigger high-altitude pulmonary oedema in humans. *SchweizMedWochenschr* 2000; **130(11):**385–9.
29 Staub NC. Pulmonary edema. *Physiol Rev* 1974; **54(3):**678–811.
30 Matthay MA, Folkesson HG, Verkman AS. Salt and water transport across alveolar and distal airway epithelia in the adult lung. *Am J Physiol* 1996; **270:**L487–L503.
31 Hummler E, Barker P, Gatzy J *et al.* Early death due to defective neonatal lung liquid clearance in aENaC-deficient mice. *Nature Genet* 1996; **12:**325–8.
32 Egli M, Duplain H, Lepori M *et al.* Defective respiratory amiloride-sensitive sodium transport predisposes to pulmonary oedema and delays its resolution in mice. *J Physiol* 2004; **560(Pt 3):**857–65.
33 Knowles MR, Buntin W, Bromberg PA, Gatzy JT, Boucher RC. Measurements of transepithelial electric potential differences in the trachea and bronchi of human subjects in vivo. *Am Rev Respir Dis* 1982; **126:**108–12.
34 Sartori C, Allemann Y, Duplain H *et al.* Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med* 2002; **346(21):**1631–6.
35 Sartori C, Duplain H, Lepori M *et al.* High altitude impairs nasal transepithelial sodium transport in HAPE-prone subjects. *Eur Respir J* 2004; **23(6):**916–20.
36 Tomlinson LA, Carpenter TC, Baker EH, Bridges JB, Weil JV. Hypoxia reduces airway epithelial sodium transport in rats. *Am J Physiol* 1999; **277(5 Pt 1):**L881–6.
37 Planes C, Escoubet B, Blot-Chabaud M, Friedlander G, Farman 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(4):**508–18.
38 Sakuma T, Suzuki S, Usada K *et al.* Preservation of alveolar epithelial fluid transport mechanisms in the rewarmed human lung after severe hypothermia. *J Appl Physiol* 1996; **80:**1681–6.
39 Sartori C, Vollenweider L, Loffler BM *et al.* Exaggerated endothelin release in high-altitude pulmonary edema. *Circulation* 1999; **99(20):**2665–8.