

New Insights in the Pathogenesis of High-Altitude Pulmonary Edema

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Abstract

High-altitude pulmonary edema is a life-threatening condition occurring in predisposed but otherwise healthy individuals. It therefore permits the study of underlying mechanisms of pulmonary edema in the absence of confounding factors such as coexisting cardiovascular or pulmonary disease, and/or drug therapy.

There is evidence that some degree of asymptomatic alveolar fluid accumulation may represent a normal phenomenon in healthy humans shortly after arrival at high altitude. Two fundamental mechanisms then determine whether this fluid accumulation is cleared or whether it progresses to HAPE: the quantity of liquid escaping from the pulmonary vasculature and the rate of its clearance by the alveolar respiratory epithelium. The former is directly related to the degree of hypoxia-induced pulmonary hypertension, whereas the latter is determined by the alveolar epithelial sodium transport. Here, we will review evidence that, in HAPE-prone subjects, impaired pulmonary endothelial and epithelial NO synthesis and/or bioavailability may represent a central underlying defect predisposing to exaggerated hypoxic pulmonary vasoconstriction and, in turn, capillary stress failure and alveolar fluid flooding. We will then demonstrate that exaggerated pulmonary hypertension, although possibly a *conditio sine qua non*, may not always be sufficient to induce HAPE and how defective alveolar fluid clearance may represent a second important pathogenic mechanism. (Prog Cardiovasc Dis 2010;52:485–492)

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High-altitude pulmonary edema is a life-threatening condition occurring in predisposed but otherwise healthy individuals. It thereby allows studying underlying mechanisms of pulmonary edema in the absence of confounding factors, such as coexisting cardiovascular or pulmonary disease, and/or drug therapy. Pulmonary edema results from a persistent imbalance between forces that drive water into the airspace of the lung and the biological mechanisms for its removal.^{1,2} There is evidence that some degree of asymptomatic alveolar fluid accumulation may represent a normal phenomenon in healthy humans shortly after arrival at high altitude.³ Two fundamental mechanisms then determine whether this fluid accumulation is cleared or whether it progresses to HAPE. After arrival at high altitude, the amount of

alveolar fluid depends on the quantity of liquid escaping from the pulmonary vasculature on the one hand and on the rate of its reabsorption by the alveolar respiratory epithelium on the other hand. The former is directly related to the degree of hypoxia-induced pulmonary hypertension, whereas the latter is determined by the alveolar epithelial sodium transport. Over the past decade, it has been established that HAPE represents a prototype of a distinct form of pulmonary edema in humans, resulting from the conjunction of alveolar fluid flooding induced by exaggerated hypoxic pulmonary hypertension and impaired alveolar fluid clearance related to defective pulmonary transepithelial sodium transport. In the following, we will review this evidence.

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Exaggerated hypoxic pulmonary hypertension

Exaggerated pulmonary hypertension is a hallmark of HAPE,^{4,5} and several observations indicate that it

Abbreviations and Acronyms**ET-1** = Endothelin-1**HAPE** = High-altitude pulmonary edema**NO** = nitric oxide**PFO** = patent foramen ovale

ties that facilitate pulmonary hypertension are risk factors for developing HAPE at relatively low altitude (1500–2500 m). Lowering of pulmonary artery pressure with pharmacologic agents of different types has beneficial effects in HAPE.¹⁰ Most importantly, pharmacologic prevention of exaggerated pulmonary hypertension in HAPE-prone subjects reduces the incidence of pulmonary edema during high-altitude exposure.^{11,12}

To cause pulmonary edema, the elevated pulmonary-artery pressure has to be transmitted to the capillaries. For this to occur, one has to postulate that there exist

contributes to its pathogenesis. Anatomical (congenital absence of the right pulmonary artery, pulmonary artery occlusion from granulomatous mediastinitis)^{6,7} or functional (Down syndrome)^{8,9} abnormalities

pulmonary regions where capillaries are not protected by constricted resistance vessels. This appears to be the case because, in patients suffering from HAPE, the perfusion of regions of the lung with radiographic evidence of pulmonary edema is much greater than the one of the regions without edema (Fig 1).¹³ Consistent with this concept, pulmonary capillary pressure is considerably higher in patients with HAPE than in those without pulmonary edema.¹⁴ Using the arterial occlusion method, which most likely measures pressures in vessels close to 100 μ m in diameter, we found that, at 4559 m, pulmonary capillary pressure was on average 16 mm Hg (range, 14–18 mm Hg) in HAPE-prone subjects who did not develop pulmonary edema and 22 mm Hg (range, 20–26 mm Hg) in those who developed HAPE. These findings suggest that, in HAPE-prone subjects, the pulmonary capillary pressure threshold value for alveolar fluid flooding is roughly 20 mm Hg. It is possible that, in addition to inhomogeneous hypoxic pulmonary vasoconstriction resulting in regional overperfusion of capillaries in nonprotected areas,

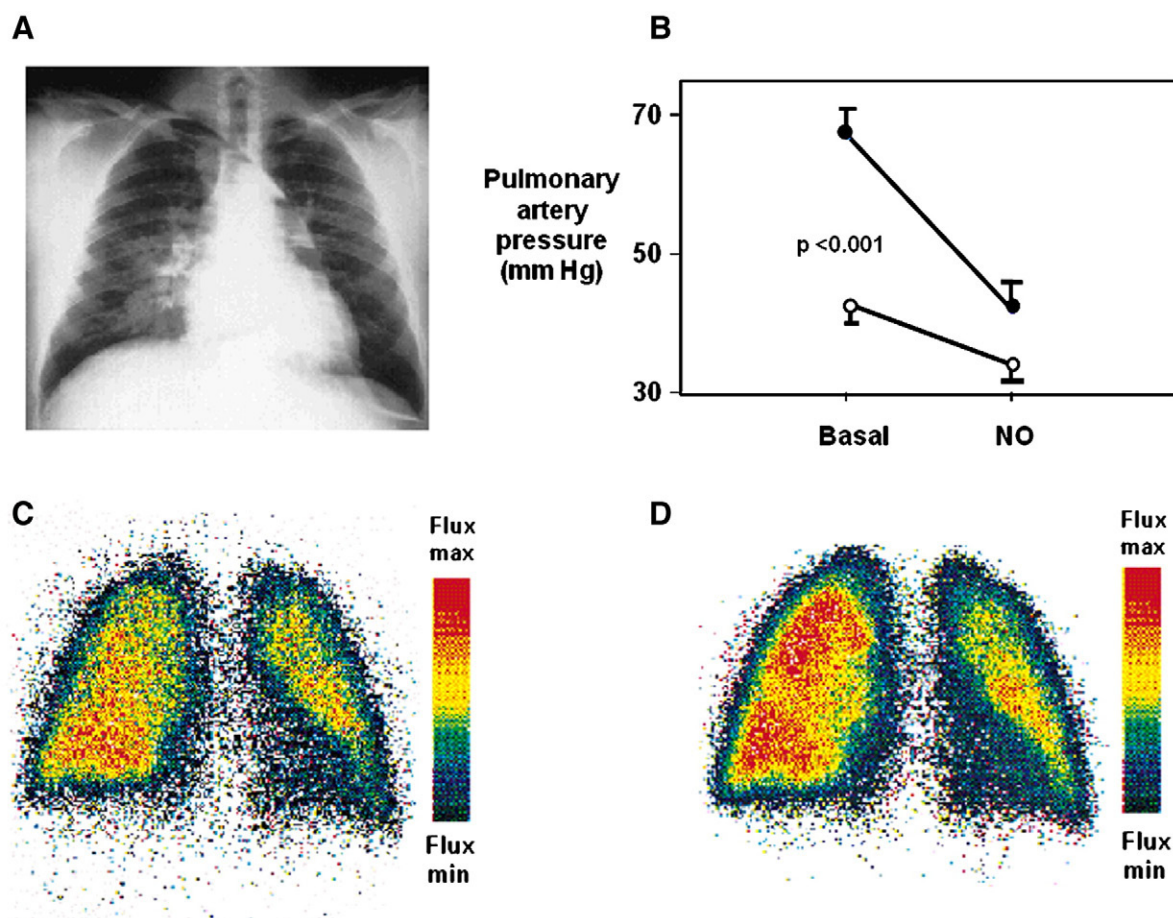


Fig 1. Effects of NO inhalation on pulmonary blood flow and systolic pulmonary-artery pressure in HAPE-prone subjects. The chest x-ray film (A) was obtained a few minutes before the first lung-perfusion scan (B) was obtained. The second scan (D) was obtained 20 minutes after the start of NO inhalation (40 ppm). The inhalation of NO, which induced a significantly greater reduction of the pulmonary-artery pressure in HAPE-prone than HAPE-resistant subjects (C), redistributed blood flow away from edematous regions of the lungs and toward nonedematous regions (adapted from Scherrer et al¹³).

hypoxia-induced constriction of pulmonary veins,¹⁵ leading to increased vascular resistance downstream to the site of fluid filtration,¹⁶ also contributes to the exaggerated increase in capillary pressure.

An exaggerated increase of pulmonary capillary pressure would be expected to result in a high-permeability-type pulmonary edema. In line with this hypothesis, in individuals with incipient HAPE, bronchoalveolar lavage fluid analysis revealed leakage of erythrocytes and large-molecular-weight proteins. These findings indicate capillary stress failure and demonstrate that, in its early stage, HAPE is a high-pressure-mediated permeability type of pulmonary edema. Inflammation does not appear to contribute to HAPE in its initial stage because alveolar macrophages, leukocytes, proinflammatory cytokines, and eicosanoids in the bronchoalveolar lavage¹⁷ and exhaled NO, a marker of alveolar inflammation,¹⁸ are absent or normal in patients with incipient HAPE.

Mechanisms of exaggerated pulmonary hypertension in HAPE

Defective pulmonary NO synthesis

Nitric oxide plays a major role in the regulation of pulmonary vascular tone in animals and humans. In normal humans, inhibition of NO synthesis by N^G-monomethyl-L-arginine infusion potentiates the hypoxic pulmonary vasoconstrictor response,¹⁹ whereas NO inhalation attenuates this response.²⁰ At high altitude, we examined the effects of NO inhalation on pulmonary-artery pressure in HAPE-prone mountaineers and subjects resistant to this condition.¹³ As expected, HAPE-prone subjects had more pronounced pulmonary vasoconstriction than those resistant to such edema. During NO inhalation, however, pulmonary-artery pressure was similar in both groups because the NO-induced decrease in pulmonary-artery pressure was much larger in HAPE-prone subjects (Fig 1C). This suggests that defective pulmonary endothelial NO synthesis is one of the mechanisms contributing to exaggerated hypoxic pulmonary hypertension in HAPE-prone individuals. Consistent with this concept, HAPE susceptibility is associated with endothelial NO synthase polymorphisms and impaired vascular NO synthesis in some populations,^{21,22} whereas in populations characterized by attenuated hypoxic pulmonary vasoconstriction (and presumably relative resistance to HAPE), endothelial NO synthase polymorphisms associated with augmented vascular NO synthesis have been reported.²³ Accordingly, increasing NO availability stimulated by the phosphodiesterase-5 inhibitor tadalafil prevented exaggerated pulmonary hypertension and pulmonary edema in a small group of HAPE-prone subjects.¹² In addition to its direct effects at the pulmonary vasculature, NO also attenuates oxidative stress, a mechanism that facilitates hypoxic pulmonary

vasoconstriction.^{24,25} Thus, in NO-deficient states, loss of NO-inhibition of oxidative stress may represent an additional mechanism contributing to exaggerated hypoxic pulmonary hypertension.

Nitric oxide is synthesized not only by the pulmonary vascular endothelium, but also by the respiratory epithelium. Respiratory epithelial NO also regulates pulmonary artery pressure.²⁶ Its synthesis can be assessed by measuring NO in the exhaled air.²⁷ In HAPE-prone subjects, short-term hypoxia decreases exhaled NO.²⁸ At high altitude, exhaled NO is considerably lower in HAPE-prone than in HAPE-resistant subjects; and there exists an inverse relationship between pulmonary-artery pressure and exhaled NO¹⁸ (Fig 2), suggesting that defective respiratory epithelial NO synthesis contributes to exaggerated hypoxic pulmonary hypertension in HAPE-prone mountaineers.

Exaggerated ET-1 synthesis

In addition to relaxing factors, the pulmonary endothelium also synthesizes vasoconstrictor factors. Endothelin-1 is the most potent among them and regulates pulmonary vascular tone during hypoxic stress.²⁹ In healthy humans, high-altitude exposure increases ET-1 plasma concentration³⁰; and the endothelin antagonist bosentan attenuates altitude-induced pulmonary hypertension.³¹ In HAPE-prone mountaineers, ET-1 plasma levels at high altitude are higher than those in mountaineers resistant to edema. Moreover, there exists a direct relationship between the altitude-induced increase in ET-1 plasma levels and systolic pulmonary-artery pressure.³² Thus, increased ET-1 synthesis and/or its reduced clearance may also contribute to exaggerated hypoxic pulmonary hypertension in HAPE-prone subjects. Interestingly, in human endothelial cells, NO inhibits the hypoxia-induced stimulation of ET-1 gene expression and synthesis,³³ suggesting that defective NO synthesis and increased ET-1 synthesis could be causally related.

Exaggerated sympathetic activation

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 dogs.³⁴ In line with these findings, at high altitude, HAPE-prone mountaineers display exaggerated sympathetic activation that is directly related to exaggerated hypoxic pulmonary hypertension.³⁵ Most importantly, the sympathetic activation precedes the development of lung edema. These data suggest that exaggerated sympathetic activity contributes to exaggerated hypoxic pulmonary hypertension and pulmonary edema in HAPE-prone subjects. Interestingly, NO buffers sympathetic outflow in experimental animals and in humans,³⁶ suggesting that defective NO synthesis may

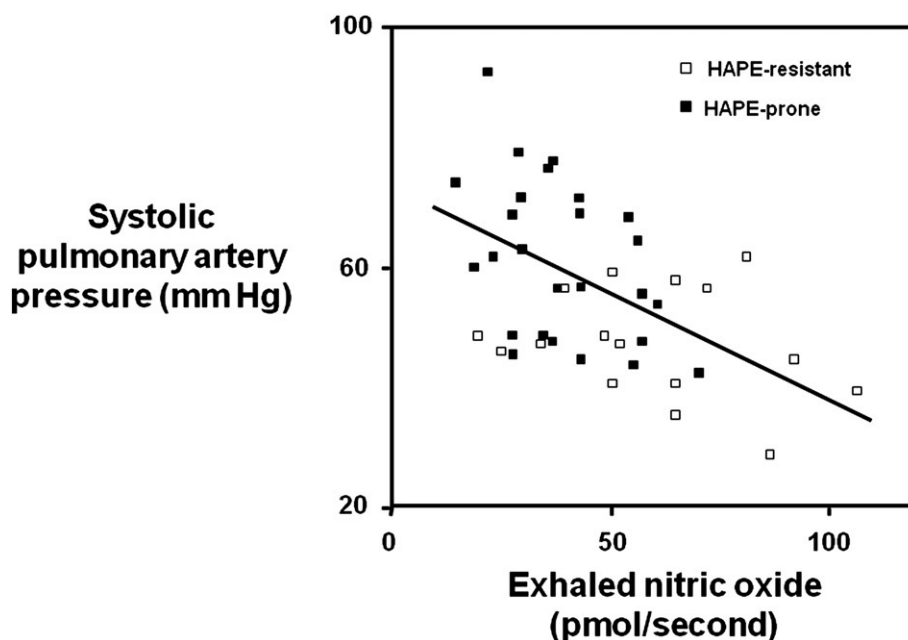


Fig 2. Relationship between exhaled NO and systolic pulmonary-artery pressure in HAPE-prone and HAPE-resistant mountaineers at high altitude. An impairment of respiratory epithelial NO synthesis was associated with greater hypoxic pulmonary vasoconstriction ($r = 0.51$, $P < .001$) (adapted from Duplain et al¹⁸).

contribute to exaggerated altitude-induced sympathetic activation in HAPE-prone subjects.

Recent data suggest that dexamethasone prevents pulmonary hypertension and pulmonary edema in HAPE-prone subjects, but the mechanism is unknown.¹² It is well established that dexamethasone prevents insulin- and alcohol-induced sympathetic activation in humans by a central neural mechanism.^{37,38} It is tempting to speculate that, in HAPE-prone subjects, dexamethasone prevents exaggerated pulmonary hypertension and pulmonary edema by preventing hypoxia-induced sympathetic vasoconstrictor activation.

Patent foramen ovale

Subjects prone to HAPE are characterized by exaggerated altitude-induced hypoxemia that is present before the occurrence of pulmonary edema and has been attributed to relative hypoventilation,³⁹ an augmented alveoloarterial oxygen gradient, or intrapulmonary or intracardiac right-to-left shunting.⁴⁰ With regard to the latter, anecdotal evidence suggested that intracardiac shunting across a PFO may exacerbate hypoxemia in HAPE.⁴¹ In a recent study, PFO was found to be 4 to 5 times more frequent in HAPE-prone participants than in mountaineers resistant to this condition.⁴² Most importantly, at high altitude, spontaneous right-to-left-shunting was present in HAPE-prone participants with large PFOs; and the arterial hypoxemia was more pronounced in these

subjects than in those with small or no PFO, suggesting that the size of the PFO, rather than its mere presence, may be clinically relevant in this setting. Observations made in divers with decompression illness⁴³ and patients with platypnea-orthodeoxia are in line with this hypothesis.⁴⁴ These findings suggest the new concept that, in HAPE-prone individuals with PFO, the acute hypoxic pulmonary vasoconstriction initiates a vicious cycle by causing right-to-left shunting across a PFO that in turn aggravates hypoxemia, resulting in reduced mixed venous oxygen tension, greater alveolar hypoxia, and greater pulmonary hypertension.⁴⁵

In summary, HAPE-prone individuals are characterized by exaggerated pulmonary hypertension that is related, at least in part, to pulmonary endothelial and epithelial dysfunction and sympathetic overactivation. Defective NO synthesis and/or decreased NO bioavailability may represent a central underlying mechanism in the pathogenesis of this exaggerated hypoxic pulmonary hypertension (Fig 3). Recent evidence suggests that, in some HAPE-prone individuals, right-to-left shunting across a PFO may represent an additional mechanism underpinning this exaggerated response.

Although the studies summarized above have led to a better understanding of the underlying mechanisms and the role of exaggerated hypoxic pulmonary hypertension in the pathogenesis of HAPE, recent evidence indicates that exaggerated pulmonary hypertension is not always

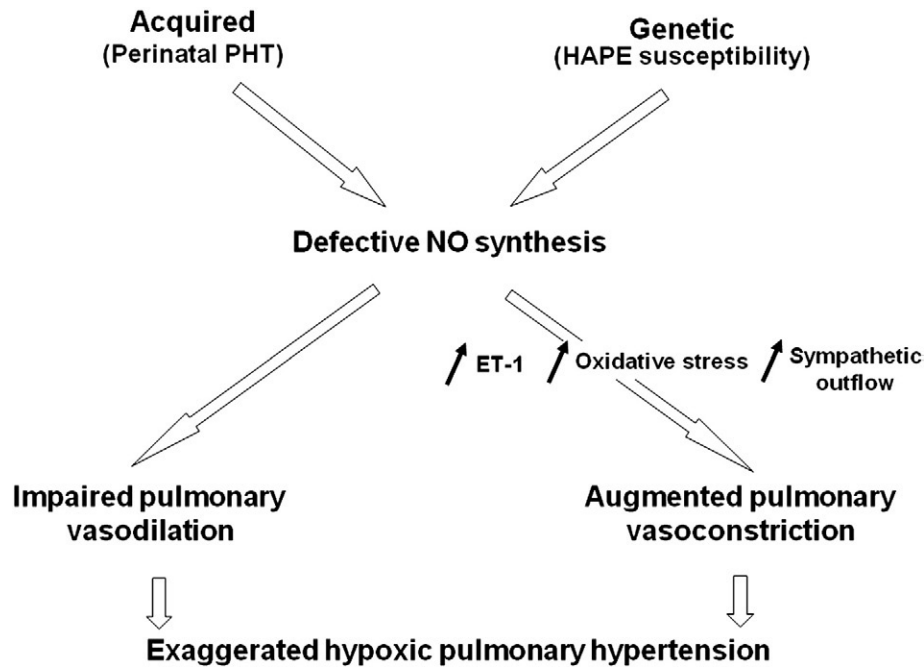


Fig 3. Schematic representation of the central role of defective NO synthesis (and/or bioavailability) in the pathogenesis of exaggerated hypoxic pulmonary hypertension and HAPE.

sufficient to trigger HAPE and that additional mechanisms need to play a role.

Exaggerated pulmonary hypertension per se is not sufficient to trigger HAPE

In a recent study on the fetal/perinatal programming of pulmonary vascular dysfunction at the high-altitude research laboratory Capanna Regina Margherita in the

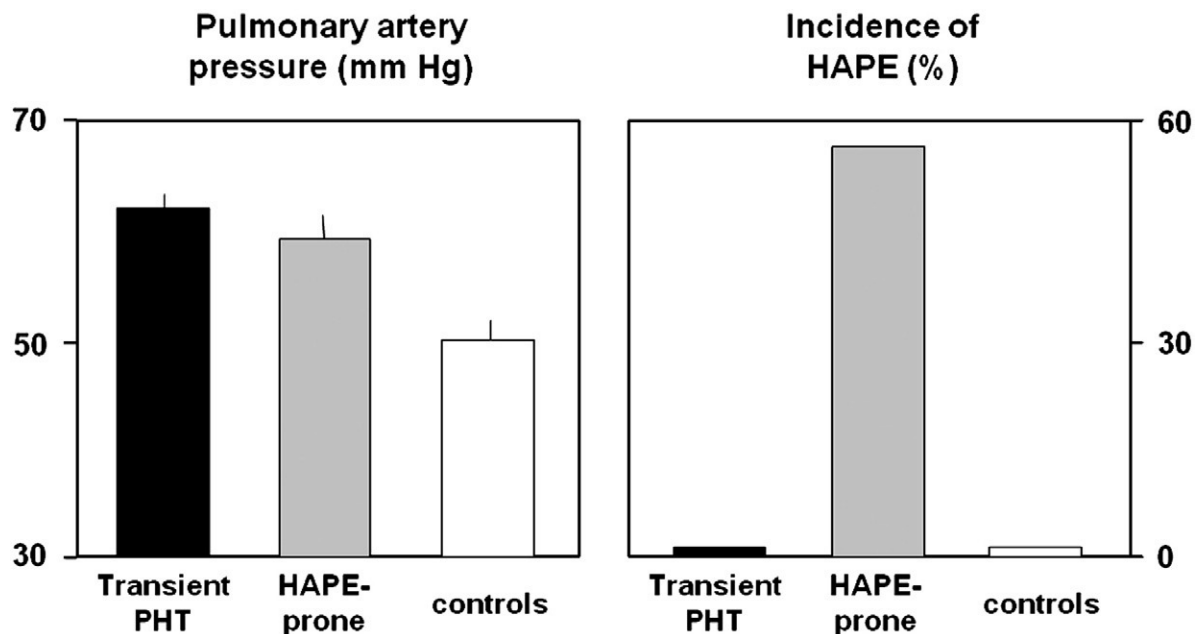


Fig 4. Pulmonary-artery pressure and incidence of HAPE in 18 HAPE-prone mountaineers, 10 healthy young adults with a history of transient perinatal pulmonary hypertension, and 17 HAPE-resistant control subjects at 4559 m (adapted from Sartori et al^{46,47}).

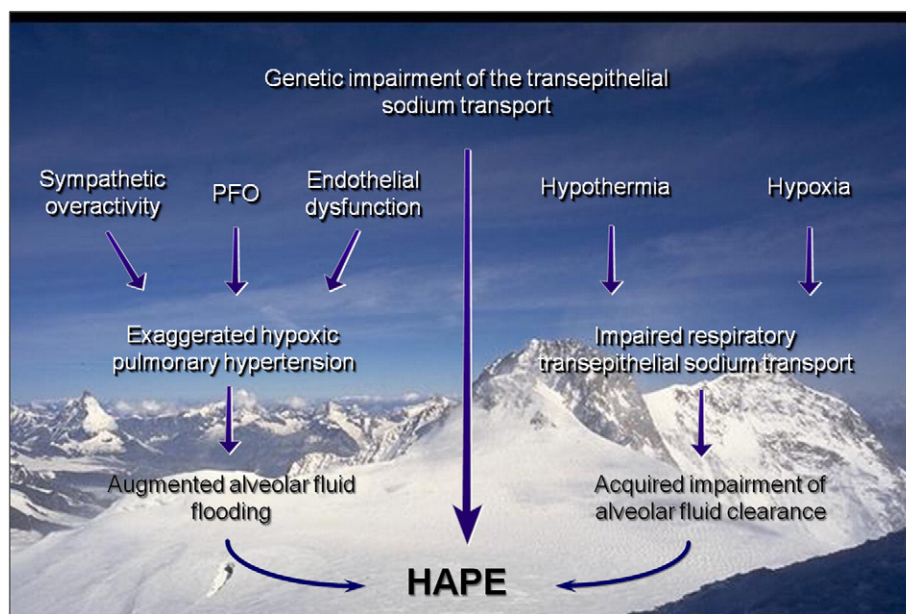


Fig 5. Pathogenesis of HAPE.

Alps (4559 m), we found that young healthy adults who had suffered from transient lack of oxygen during the first few days after birth display exaggerated hypoxic pulmonary hypertension of similar magnitude as the one observed in HAPE-prone subjects studied at this same altitude location⁴⁶ (Fig 4). Surprisingly, however, none of these subjects developed HAPE⁴⁷ (Fig 4), indicating that exaggerated pulmonary hypertension per se is not always sufficient to trigger HAPE and that additional mechanisms play a role. In subsequent studies, we provided direct evidence that impaired alveolar fluid clearance related to a defect of the transepithelial respiratory sodium transport represents such an additional mechanism.^{48,49}

Defective alveolar transepithelial sodium transport predisposes to HAPE

Pulmonary edema results from an imbalance between fluid leaking into the airspace and its removal. As detailed elsewhere in this issue (Sartori et al), data in genetically engineered mice demonstrate that defective respiratory sodium transport facilitates pulmonary edema.

We wondered whether a similar defect could predispose to HAPE. We found that, in HAPE-prone subjects, transepithelial respiratory sodium transport is defective⁴⁸ and that this defect is further aggravated during high-altitude exposure.⁵⁰ β -Adrenergic agonists stimulate transepithelial sodium transport and alveolar fluid clearance in experimental animal models.⁵¹ To examine the importance of defective respiratory sodium transport in the pathogenesis of HAPE, we therefore studied whether

pharmacologic stimulation of this transport decreases the incidence of HAPE in susceptible subjects. We found that prophylactic stimulation of this transport with a β -adrenergic agonist decreased the incidence of HAPE in highly susceptible subjects by more than 50%.⁴⁸ In line with this concept, β -adrenergic stimulation of respiratory transepithelial sodium transport was subsequently found to decrease extravascular lung water in patients with acute respiratory distress syndrome⁵² and accelerate the resolution of pulmonary edema after lung resection.⁵³

Taken together, these very important new findings demonstrate that exaggerated pulmonary hypertension per se, although possibly a *conditio sine qua non*, is not always sufficient to trigger HAPE and establish the novel concept that, in HAPE-susceptible subjects, an additional defect, namely, impaired respiratory transepithelial sodium and water transport, contributes to the pathogenesis of pulmonary edema.

Conclusion

Based on our results, we suggest the following new concept for the pathogenesis of HAPE (Fig 5). Pulmonary edema 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 is augmented because of exaggerated pulmonary hypertension that appears to be related, at least in part, to defective NO synthesis leading to endothelial dysfunction and exaggerated sympathetic activation. Exaggerated pulmonary hypertension per se,

however, is not sufficient to trigger HAPE. Our findings indicate that HAPE-prone subjects are characterized by a defect, possibly genetic, of the transepithelial sodium (and water) transport that during high-altitude exposure may be further impaired by environmental factors such as hypoxia and cold temperature. The conjunction of these pulmonary vascular endothelial and alveolar epithelial defects ultimately leads to HAPE.

Last but not least, studies in HAPE have shed new light on the understanding of hypoxia-related disease states in general. For example, these studies have shown the key role played by sodium-transport–driven alveolar fluid clearance in the pathogenesis of pulmonary edema and established defective alveolar epithelial and pulmonary endothelial NO synthesis as a pivotal event in the pathogenesis of exaggerated hypoxic pulmonary vasoconstriction.

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Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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