

HIGHLIGHTED TOPIC | Pulmonary Circulation and Hypoxia

Physiological aspects of high-altitude pulmonary edema

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Physiological aspects of high-altitude pulmonary edema. *J Appl Physiol* 98: 1101–1110, 2005; doi:10.1152/jappphysiol.01167.2004.—High-altitude pulmonary edema (HAPE) develops in rapidly ascending nonacclimatized healthy individuals at altitudes above 3,000 m. An excessive rise in pulmonary artery pressure (PAP) preceding edema formation is the crucial pathophysiological factor because drugs that lower PAP prevent HAPE. Measurements of nitric oxide (NO) in exhaled air, of nitrites and nitrates in bronchoalveolar lavage (BAL) fluid, and forearm NO-dependent endothelial function all point to a reduced NO availability in hypoxia as a major cause of the excessive hypoxic PAP rise in HAPE-susceptible individuals. Studies using right heart catheterization or BAL in incipient HAPE have demonstrated that edema is caused by an increased microvascular hydrostatic pressure in the presence of normal left atrial pressure, resulting in leakage of large-molecular-weight proteins and erythrocytes across the alveolarcapillary barrier in the absence of any evidence of inflammation. These studies confirm in humans that high capillary pressure induces a high-permeability-type lung edema in the absence of inflammation, a concept first introduced under the term “stress failure.” Recent studies using microspheres in swine and magnetic resonance imaging in humans strongly support the concept and primacy of nonuniform hypoxic arteriolar vasoconstriction to explain how hypoxic pulmonary vasoconstriction occurring predominantly at the arteriolar level can cause leakage. This compelling but as yet unproven mechanism predicts that edema occurs in areas of high blood flow due to lesser vasoconstriction. The combination of high flow at higher pressure results in pressures, which exceed the structural and dynamic capacity of the alveolar capillary barrier to maintain normal alveolar fluid balance.

pulmonary artery pressure; hypoxic pulmonary vasoconstriction; nitric oxide; inflammation; alveolar fluid clearance; pathophysiology; review

CLINICAL PICTURE

High-altitude pulmonary edema (HAPE) is noncardiogenic pulmonary edema that usually occurs at altitudes above 3,000 m in rapidly ascending nonacclimatized individuals within the first 2–5 days after arrival. It may also occur in high-altitude dwellers who return from sojourns at low altitude. The first medical description of HAPE was published in Peru and recognized the latter form, also called reentry HAPE, as a pulmonary edema associated with electrographic signs of right ventricular overload (67). The first cases of HAPE in unacclimatized lowlanders climbing to high altitude were reported from the Rocky Mountains (53). The two forms very probably share the same pathophysiology.

The reader is referred to other reviews (9, 41, 96, 97) for an extensive presentation of the clinical picture. In this review, we

point out some particular characteristics that might elucidate the underlying pathophysiology and are revealed by classical and newly evolving pathophysiological concepts.

The prevalence of HAPE depends on the degree of susceptibility, the rate of ascent, and the final altitude. At an altitude of 4,500 m, the prevalence may vary depending on the rate of ascent between 0.2 and 6% in an unselected population (13) and at 5,500 m between 2 and 15% (40, 100). Mountaineers who develop HAPE at altitudes between 3,000 and 4,500 m have a 60% recurrence rate when ascending rapidly to these altitudes (13). On the other hand, susceptible mountaineers can ascend up to 7,000 m without developing HAPE when ascent rate is slow, with an average gain of altitude of 300–350 m/day above 2,000 m (9). Even more astonishing is the fact that a mountaineer who develops HAPE and descends to recover can reascend to even higher altitudes a few days after recovery without developing HAPE again (66). There is most likely no complete “resistance” to HAPE. Episodes of HAPE in experienced, successful high-altitude climbers demonstrate that most likely everyone can get HAPE when ascending fast and high enough (9). It is also important to note that the setting in which

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HAPE occurs usually involves heavy and prolonged exercise and that there seems to be a male predominance (55).

Chest X-ray and computerized tomography (CT) scans in early HAPE show a patchy peripheral distribution of edema as shown in Fig. 1. The radiographic appearance of HAPE is more homogenous and diffuse in advanced cases and during recovery (112, 113). Moreover, in patients who had two episodes of HAPE, the similarity of the radiographic appearance between the two periods was random, suggesting that structural abnormalities do not account for edema location (112), except in those with congenital unilateral absence of a pulmonary artery, in whom the edema always occurs in the contralateral lung (39).

Autopsies reveal distended pulmonary arteries and diffuse pulmonary edema with bloody foamy fluid present in the airways but no evidence of left ventricular failure (7, 77). In addition, hyaline membranes were found in most cases and arteriolar thrombi, pulmonary hemorrhages, or infarcts were often present.

CHARACTERISTICS OF SUSCEPTIBLE INDIVIDUALS

It is well known that individuals who develop HAPE at altitudes of 4,000 m show an abnormal increase in pulmonary artery pressure (PAP) during brief or prolonged hypoxic exposure (38, 54, 110). Interestingly, they also have a greater PAP rise during exercise in normoxia (Fig. 2) (34, 38, 61), pointing to a constitutionally generalized hyperreactivity of the pulmonary circulation. Furthermore, most HAPE-susceptible individuals have a low hypoxic ventilatory response (HVR) (42, 47, 72), which leads to a low alveolar P_{O_2} and thus a greater stimulus to HPV at any given altitude. The hypothesis that polymorphisms of the tyrosine hydroxylase gene leading to decreased peripheral chemoreceptor dopamine synthesis might be associated with blunted HVR and susceptibility to HAPE could not be confirmed in Japanese mountaineers (45). Evidence in support of reduced peripheral chemosensitivity to hypoxia contributing to greater HPV comes from studies where carotid body resection and/or denervation of the lung increases

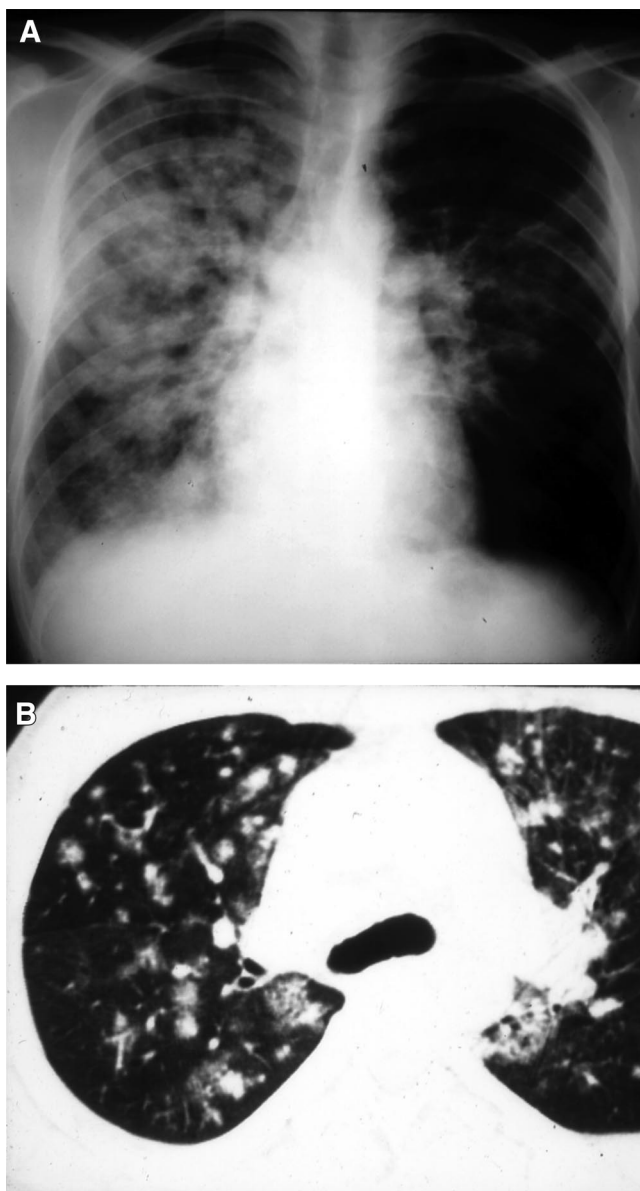


Fig. 1. A: radiograph of a 37-yr-old male mountaineer with high-altitude pulmonary edema (HAPE) that shows a patchy to confluent distribution of edema, predominantly on the right side. B: computerized tomography scan of 27-yr-old mountaineer with recurrent HAPE showing patchy distribution of edema.

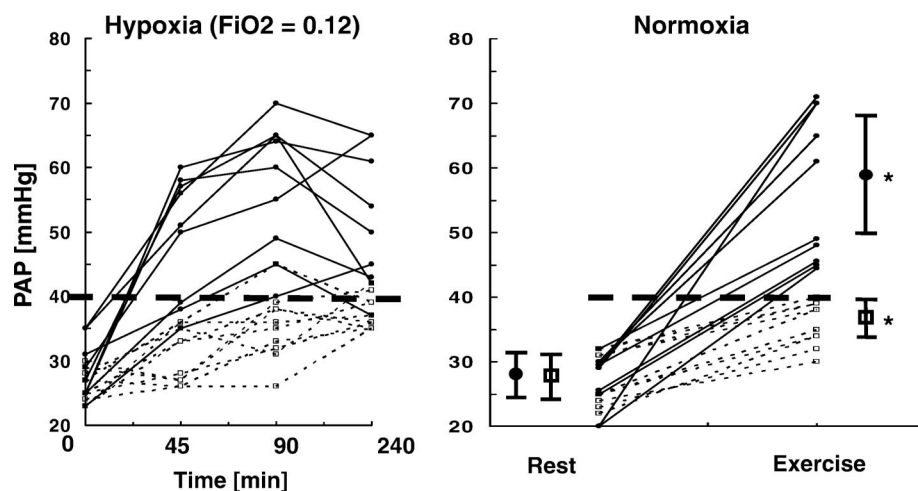


Fig. 2. Pulmonary artery pressure (PAP) in HAPE-susceptible individuals (solid lines and filled symbols) and in nonsusceptible controls (dashed lines and open symbols) during exposure to normobaric hypoxia (*left*) and before and during exercise on a bicycle ergometer (*right*). Highest PAP recordings during exercise (75–150 W) are shown. FiO_2 , fraction of inspired O_2 . Data from Ref. 38. * $P < 0.005$ compared with preexercise values within groups and with postexercise values between groups.

HPV at a constant alveolar PO_2 (24, 118). HAPE-susceptible individuals also have 10–15% lower lung volumes (34, 101, 110), which may contribute to increased PAP in hypoxia or exercise by causing greater alveolar hypoxia. Also lower lung volumes may cause greater pulmonary vascular resistance by virtue of a smaller vascular bed and less vascular recruitability as shown by diminished increases in diffusing capacity with exercise compared with HAPE-resistant individuals (101).

MECHANISMS ACCOUNTING FOR ENHANCED HPV

Decreased nitric oxide (NO) concentrations in exhaled air were found in HAPE-susceptible individuals during a 4-h hypoxic exposure at low altitude (20) and during the development of HAPE at high altitude (Fig. 3) (29). Furthermore, concentrations of nitrate and nitrite in bronchoalveolar lavage fluid were lower in mountaineers who developed HAPE compared with controls (105), and inhalation of 15–40 ppm NO lowered PAP and improved gas exchange in subjects with HAPE to values measured in controls (5, 95). A recent investigation of our collaborative study group in Heidelberg demonstrates an impaired endothelium-dependent vasodilator response to acetylcholine in hypoxia measured by forearm venous occlusion plethysmography in HAPE-susceptible vs. nonsusceptible controls (19a). Taken together, these data suggest that hypoxia impairs endothelial function in HAPE-sus-

ceptible individuals and results in decreased bioavailability of NO and its second messenger cGMP, which is likely to contribute to the enhanced hypoxic pulmonary vasoconstriction in HAPE. Furthermore, our observation that susceptibility to HAPE is associated with an abnormal rise of PAP to exercise in normoxia (38, 61) might be explained by an impaired endothelial NO release in response to increased blood flow in the pulmonary circulation. In accordance with this concept, the phosphodiesterase-5 inhibitors sildenafil or tadalafil, which increase the cGMP in lung tissue by inhibition of its degradation, lower PAP and improve exercise capacity at high altitude (36, 87) and prevent HAPE (68).

In addition, the latter study demonstrated that 2×8 mg dexamethasone daily starting 2 days before ascending lowers PAP as much as tadalafil and prevents HAPE equally effectively (68). This is a rather unexpected finding considering the observations that HAPE developed in individuals during or shortly after treatment of AMS by dexamethasone (17; and Schoene, personal communication). Lowering PAP by dexamethasone is compatible with reduced NO availability in HAPE in hypoxia because dexamethasone can activate endothelial NO synthase by a nontranscriptional mechanism (43) and block hypoxia-induced endothelial dysfunction in organ-cultured pulmonary arteries by increasing endothelial NO synthase (eNOS) expression (76). The observation that HAPE may

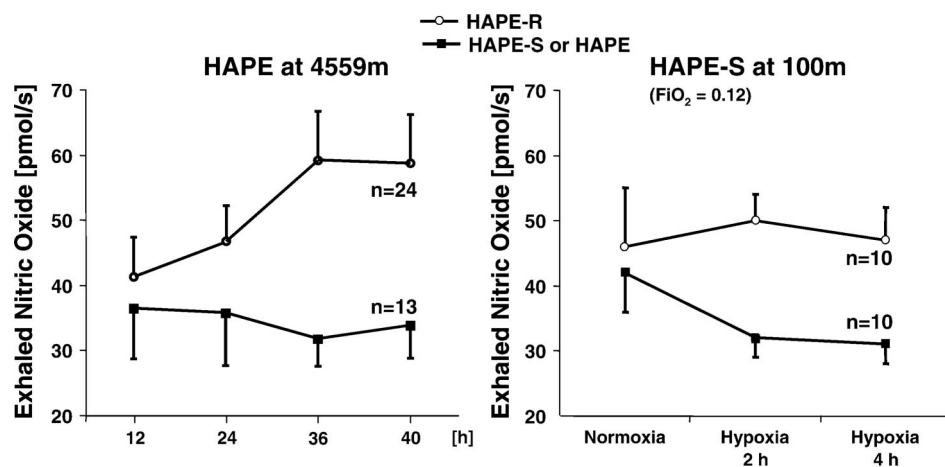


Fig. 3. *Left*: exhaled nitric oxide (NO) after 40 h at 4,559 m in individuals developing HAPE and in individuals not developing HAPE (HAPE-R) despite identical exposure to high altitude (29). *Right*: exhaled NO in HAPE-susceptible subjects (HAPE-S) and HAPE-R individuals after 4 h of exposure to hypoxia ($FiO_2 = 0.12$) at low altitude (elevation 100 m) (20). *n*, No. of subjects.

develop in individuals despite receiving dexamethasone (17) for treatment of AMS suggests that new gene transcription-mediated protein expression is critical for prevention of HAPE and may require days rather than hours to be fully realized. In addition, other actions of dexamethasone could also contribute to its preventive effect in HAPE. By increasing surfactant phospholipid and protein secretion into the alveolar lining fluid of adult animals (120, 121), dexamethasone will reduce surface tension and microvascular transmural pressure (3). This mechanism may explain the reduction in vascular permeability in hypoxic mice treated with dexamethasone in whom no changes in PAP were reported (102). Enhanced alveolar sodium (and water) reabsorption mediated by corticosteroid-induced up-regulation of alveolar epithelial apical membrane sodium channel activity and basolateral membrane Na⁺-K⁺-ATPase activity is another highly relevant action of dexamethasone (73). Both mechanisms could indirectly contribute to a lowering of PAP by improving ventilation and/or gas exchange, thus improving alveolar and arterial Po₂. Lastly, given the results with dexamethasone, it may be fruitful to explore whether HAPE susceptibility has any link to polymorphisms in the glucocorticoid receptor that influence cardiovascular and metabolic control (27).

The concept of an endothelium predisposed to greater vasoconstriction is also supported by the fact that in the Japanese population, HAPE is positively associated with two eNOS gene polymorphisms (G894T-variant and 27-base pair variable numbers of tandem repeats), which are associated with vascular diseases such as essential hypertension and coronary heart disease (28). However, an investigation in Caucasians equivalent to the Japanese study did not find an association between susceptibility to HAPE and a number of eNOS polymorphisms, including the G894T variant (114). Ethnic or environmental differences or different linkage disequilibrium in Japanese and Caucasians could account for the discrepant results.

The observation that inhaled NO did not completely normalize PAP in HAPE-susceptible individuals, but did so in those resistant to HAPE (5, 16), indicates that impaired NO synthesis cannot fully account for the excessive pulmonary vascular reactivity in HAPE-prone subjects. It is likely that additional factors, such as increased sympathetic activity or other vasoconstrictors such as angiotensin II (15), endothelin (93), or arachadonic acid metabolites (98) contribute to the increased

PAP in HAPE-susceptible subjects. Microneurography in HAPE subjects demonstrates increased skeletal muscle sympathetic activity during hypoxia at low altitudes and before HAPE at high altitudes (30). In accordance with these findings, increased plasma and/or urinary levels of norepinephrine, compared with controls, were found to precede (15) and accompany (15, 62) HAPE. Both animal and human data (75, 108) support the notion that increased sympathetic activity contributes to the greater HPV. In this fashion HAPE may bear some resemblance to neurogenic pulmonary edema (65). Whether activation of the renin-aldosterone-angiotensin system in HAPE (15) can be attributed to increased sympathetic activity or a genetically determined response is not clear. The insertion-deletion polymorphism of the angiotensin-converting enzyme is not associated with susceptibility to HAPE in Caucasian (26) and Japanese (52) mountaineers or in Indian soldiers (64), whereas the G1517T variant of the angiotensin receptor (AT₁R) gene, a polymorphism of unknown functional significance, is associated with HAPE susceptibility in Japan (52).

In summary, individuals with susceptibility to HAPE are characterized by an excessive rise in PAP in hypoxia, which can in part be attributed to a decreased bioavailability of NO. Increased sympathetic activity and vasoconstrictors such as endothelin and possibly arachadonic acid metabolites may also contribute to a greater hypoxic pulmonary vascular response. It is not, however, clear whether a greater sympathetic and vasoconstrictor response in HAPE-susceptible individuals vs. controls is simply caused by more severe hypoxemia or whether it indicates an exaggerated response to hypoxia. Arterial Po₂ is often already significantly lower in HAPE-susceptible vs. nonsusceptible individuals early during exposure in hypoxia (59).

HAPE IS A HYDROSTATIC EDEMA

Two studies performed recently at the Capanna Regina Margherita (4,559 m) in HAPE-susceptible individuals demonstrate that HAPE is caused by a noninflammatory, hydrostatic leak. Right heart catheterization showed that the abnormal rise in PAP in individuals developing HAPE is accompanied, as shown in Fig. 4, by capillary pressure increased to 20–25 mmHg (69). Thus capillary pressure exceeds a threshold value for edema formation (17–24 mmHg) established in

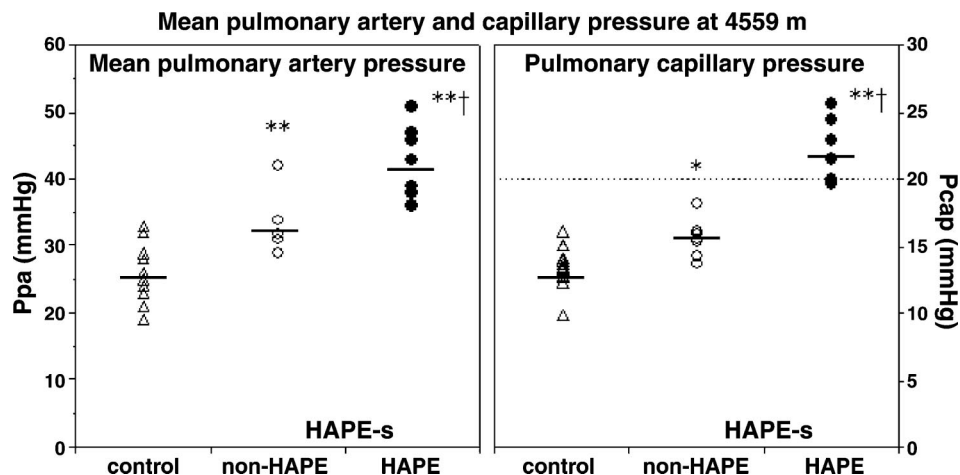


Fig. 4. Mean pulmonary artery pressure (Ppa) and pulmonary capillary pressure (Pcap) in 14 controls and in 16 HAPE-S subjects at high altitude. HAPE-S is further divided in those who developed HAPE (HAPE) and those who did not develop HAPE (non-HAPE). Bars indicate the mean values in each group. **P* < 0.05, ***P* < 0.01 vs. control, †*P* < 0.01 vs. non-HAPE. Data from Ref. 69.

dog models of lung edema (48). Bronchoalveolar lavage (BAL) performed within 1 day of ascent to 4,559 m reveals elevated red blood cell counts and serum-derived protein concentration in BAL fluid (Table 1), both in subjects with HAPE and in those who develop HAPE within the next 24 h (105). There was, however, no increase in alveolar macrophages, neutrophils, or the concentration of various proinflammatory mediators [interleukin (IL)-1, tumor necrosis factor- α , IL-8, thromboxane, prostaglandin E₂ and leukotriene B₄ (LTB₄)] at high altitude, and there was no difference between individuals resistant and susceptible to HAPE in these parameters. These data indicate that there is a partial disruption of the alveolar capillary barrier that is not caused by an inflammatory process.

BAL in more advanced HAPE (and sometimes many days after onset) showed in some, but not all cases, elevated proinflammatory cytokines, LTB₄, and increased granulocytes (63, 98). Furthermore, urinary leukotriene E₄ excretion was increased in patients with HAPE reporting to clinics in the Rocky Mountains (60). These observations suggest that inflammation may occur as a consequence of alveolar edema and microvascular disruption, which may then secondarily enhance capillary permeability.

MECHANISMS ACCOUNTING FOR INCREASED CAPILLARY PRESSURE

As pointed out above, HAPE-susceptible individuals exhibit an abnormal heightened PAP response when exposed to hypoxia (38, 54, 110). Furthermore, the excessive rise in PAP precedes HAPE (14). Cardiac catheterization of untreated cases of HAPE at high altitude revealed mean pulmonary artery pressures of 60 (range 33–117 mmHg) (6, 56, 69, 83), whereas pulmonary wedge pressures were normal. Estimations of systolic PAP by echocardiography revealed values between 50 and 80 mmHg for subjects with HAPE and 30 and 50 mmHg for healthy controls (14, 79, 95, 105). Furthermore, drugs such as nifedipine (14) and tadalafil (68), which lower PAP, prevent HAPE, and are effective for treatment (79).

Table 1. *Bronchoalveolar lavage in HAPE: differential cell count and protein concentrations*

	550 m		4,559 m		
	Con (n = 8)	HAPE-S (n = 9)	Con (n = 8)	HAPE-S (well) (n = 6)	HAPE-S (ill) (n = 3)
White blood cell count, 10 ³ /ml	8.1	6.3	9.5	8.1	9.8
Macrophages, %	94	95	83	82	85
Neutrophils, %	1	0	0	0	1
Red blood cells, %					
of total BAL cells	1	4	6	51*	74*
Total protein, mg/dl	1	2	14	34	163*
Total protein, % of plasma protein	1	3	20	48	232
PAP systolic, mmHg	22	26	37*	61*	81*

Bronchoalveolar lavage (BAL) at 550 m and on the 2nd day at 4,559 m in 8 control subjects (Con) and in 9 high-altitude pulmonary edema-susceptible subjects (HAPE-S), of whom 3 had pulmonary edema at the time of BAL. Of those 6 HAPE-S without pulmonary edema at the time of BAL, 4 developed HAPE within 18 h after BAL. * $P < 0.05$ vs. 550 m. Total protein, % of plasma protein is based on a dilution factor of 100, which has been calculated for this lavage technique and an average plasma protein of 70 g/l (105).

Because capillary pressure is also elevated in HAPE, the question arises how hypoxic constriction of arterioles can lead to edema. Three mechanisms have been suggested: transarteriolar leakage, irregular vasoconstriction with regional overperfusion, and hypoxic venoconstriction.

There is evidence in hypoxic animal experiments using the double-occlusion technique (44, 89) that the small arterioles are exposed to high pressure and that they are the site of transvascular leakage in the presence of markedly increased PAP in hypoxia (117). Pulmonary veins also contract in response to hypoxia (86, 122), increasing the resistance downstream of the fluid filtration region. Both mechanisms, alone or in combination, however, cannot explain the patchy radiographic appearance of early HAPE as it appears on chest radiographs or CT scans, unless we postulate in addition regional heterogeneity of hypoxic pulmonary vasoconstriction.

If vasoconstriction in hypoxia is inhomogeneous, HAPE could be the consequence of uneven distribution of blood flow. High flow in areas with low vasoconstriction would lead to increased capillary pressure due to venous resistance as demonstrated in animal experiments by Younes et al. (119) and a longitudinal pressure drop across these vessels insufficient to lower the tension below the threshold of 17–24 mmHg at the point of entry into the alveolar microvasculature (48). This concept of increased capillary pressure by a high blood flow was postulated by Visscher (109) first and adapted to HAPE by Hultgren (57). Recent investigations, which demonstrate that hypoxic pulmonary vasoconstriction is uneven, give substantial support to the concept of regional overperfusion. With the use of microspheres, it was shown that the spatial heterogeneity of the pulmonary perfusion in pigs increases with hypoxia (46). Furthermore, a study using magnetic resonance imaging found larger blood flow heterogeneity in hypoxia in HAPE-susceptible individuals vs. nonsusceptible controls (49).

In summary, these most recent investigations provide evidence for the concept that a high blood flow accounts for the increased capillary pressure because it exceeds the capacity of dilation of the capillary-venous side (119). Pulmonary edema due to high blood flow can occur in nonoccluded areas in pulmonary embolism (58), following thromboendarterectomy (74), and it contributes to pulmonary edema during vigorous exercise in highly trained athletes (21, 50) or racehorses (115) that can sustain a very high cardiac output. It is quite likely that the increase in pulmonary blood flow on exercise in HAPE-susceptible individuals will raise pulmonary capillary pressure more and provoke more edema formation.

Uneven HPV might be attributed to uneven distribution of arterial smooth muscle cells. This hypothesis could account for the fact that slow ascent does not lead to HAPE even in susceptible individuals and for the observation that HAPE only occurs during the first 5 days after acute exposure to a given altitude. In both situations, rapid remodeling and generalized muscular hypertrophy of pulmonary arterioles could lead to a more even distribution of blood flow. This may contribute to persistent excessive pulmonary hypertension and lead over some weeks to months to congestive right heart failure termed “sub-acute mountain sickness” as described in Han infants in Tibet (103) and in Indian soldiers stationed at altitudes between 5,000 and 6,000 m (4).

NATURE OF THE LEAK IN HAPE

Measurements of capillary pressure (69) and analysis of BAL fluid (105) in early HAPE indicate that hydrostatic stress can lead to a permeability-type edema with high protein concentration in the absence of inflammation. This concept was first advanced in left-sided congestive heart failure (106) and extended to HAPE by West et al. (116), who coined the structural engineering term “stress failure” and went on to describe its basis in excessive stress on the collagen and other supporting extracellular matrix elements of the alveolar capillary barrier. West and colleagues (115) showed in rabbit lungs that a rapid exposure of the pulmonary microcirculation to transvascular pressures of 40–60 cmH₂O (30–44 mmHg) within 1 min is a hydraulic stress that exceeds the load-bearing limits of the membrane collagen network and results in ruptures of the basement membrane and thus the alveolar-capillary barrier. We hesitate to use the term “stress failure” that is linked to these structural changes to account for the permeability changes observed in early HAPE with only moderate capillary pressure elevation at rest and with mild-moderate exercise. Although capillary pressure may rise considerably higher during the exercise of ascending, our subjects showed no signs of pulmonary edema after arrival and abstained from exercise during the following 12–36 h, during which time HAPE developed (105). In addition to the difference regarding magnitude and mode of exposure of the pulmonary microcirculation to increased pressure, there are some observations in early HAPE that point to substantial differences between the model of stress failure and nascent HAPE. LTB₄ is elevated in edema fluid in animal models of stress failure (107) as well as in lavage fluid of elite cyclists with alveolar hemorrhage (50) and in advanced cases of HAPE (63, 98), although this is not the case in early HAPE. LTB₄ elevation may be a marker of most extreme stress that accompanies large and abrupt pressure elevation. Furthermore, we found no increase of markers of *in vivo* fibrin or thrombin formation and normal levels of β -thromboglobulin, a marker of platelet activation, in early HAPE (10, 12). If exposure of basement membranes and rupture of tissue occur, we would expect to find such activation, which occurs in very severe, advanced HAPE (11, 18).

These observations suggest that the leak in early HAPE might be caused by nontraumatic, dynamic, pressure-sensitive opening/stretching of pores, fenestrae, or increased transcellular vesicular flux, which allows plasma components to access the interstitial and then the alveolar spaces without overt damage to the barrier. Transcellular movements of plasma and its constituents via pressure-sensitive and pressure-induced continuous vesicular channels have been described in the systemic circulation (32, 78). Vesicular formation might be induced by active signaling initiated by the state of stretch on collagen and its attachments to the cell. The nature of this signaling may entail changes in intracellular calcium or cAMP concentrations, as the work of Parker and colleagues (80–82) and Adamson et al. (1) indicate. Parker et al. suggested that dynamic modulation of the vascular barrier in response to pressure changes may serve as a mechanism to release transient increases in pressure to preserve the basement membrane and collagen network so that the barrier function can rapidly be reestablished. Although the exact nature of its leak is not known, HAPE is another example of a pulmonary edema that

demonstrates that the old paradigm according to which hydrostatic stress can only lead to ultrafiltration of protein-poor fluid is too simplistic. This has also been shown for cardiogenic pulmonary edema (99) as well as in a rabbit model of cardiogenic edema (8).

ADDITIONAL CONTRIBUTING FACTORS

Exercise. Increasing cardiac output several-fold over baseline contributes to edema formation by increasing capillary pressure in overperfused areas and may even worsen the regional heterogeneity of blood flow. Furthermore, the greater increase of PAP in HAPE-susceptible individuals may impair left ventricular filling because of a ventricular septal shift shown by Ritter et al. (88) and to possible mild left ventricular stiffness arising from decreased cardiac lymph clearance to the right heart (25). Diastolic dysfunction due to pulmonary hypertension likely explains the significantly greater wedge pressure increase in HAPE-susceptible individuals compared with nonsusceptible controls during exercise in hypoxia (34), whereas at rest, wedge pressure is normal in untreated HAPE (69). In many cases of HAPE, particularly at lower elevations, exercise may be the essential component of the setting that leads to pulmonary edema.

Alveolar fluid clearance. A further mechanism that may contribute to the pathophysiology of HAPE is a diminished capacity for alveolar fluid reabsorption. The major processes that mediate water and sodium reabsorption across alveolar epithelial cells are indicated in Fig. 5A. Results obtained in cultured alveolar epithelial cells and hypoxia-exposed rats show that hypoxia 1) inhibits activity and expression of various Na transporters, the most important being apical membrane epithelial Na channels and the basolateral membrane Na⁺-K⁺-ATPase (84, 85), 2) decreases transepithelial alveolar Na transport (70), and 3) decreases the reabsorption of fluid instilled into the lung (Fig. 5B) (111). Taken together, these findings suggest that impaired clearance of fluid filtered into the alveoli may be involved in the pathophysiology of HAPE.

Alveolar epithelial sodium and fluid transport can be stimulated by β_2 -receptor agonists (for review, see Ref. 73). In addition, a recent field study shows successful prevention (~40–50% reduction) of HAPE with high-dose inhalation of the β_2 -agonist salmeterol (90). It should be noted, however, that this drug also lowers PAP as shown by the same authors (92), tightens cell-to-cell contacts (80), and increases NO production (2) as well as the ventilatory response to hypoxia (104). Any or all of these β -agonist-mediated effects could account for the protection afforded by salmeterol, independent of stimulation of Na reabsorption.

The nasal epithelium contains Na transporters similar to those of alveolar epithelium and is sometimes used as an *in vivo* model to obtain information on what might transpire at the experimentally inaccessible human alveolar epithelium. In accordance with the results obtained on alveolar cells, it has been found that nasal epithelial Na transport is also inhibited by hypoxia (71, 91). On the basis of decreased transepithelial nasal potentials in HAPE-susceptible individuals even at low altitude (71, 90), Sartori et al. (90) suggested that a decreased capacity of epithelial Na reabsorption might predispose to HAPE. However, because environmental factors and nasal dryness stimulate secretion (22) and might therefore affect

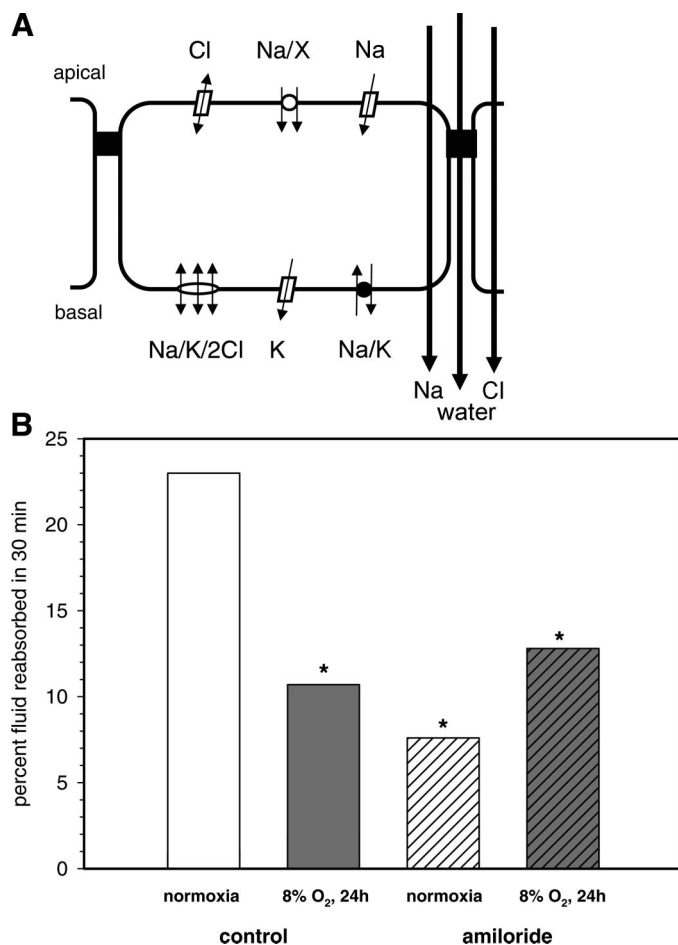


Fig. 5. Alveolar fluid balance. *A*: removal of alveolar fluid is driven by the active reabsorption of Na^+ that enters the cell via Na channels and Na-coupled transport (Na/X) and is extruded by $\text{Na}^+\text{-K}^+\text{-ATPases}$. Thus active Na reabsorption generates the osmotic gradient for the reabsorption of water. *B*: hypoxia inhibits the reabsorption of fluid instilled into lungs of hypoxia-exposed rats, which is fully explained by inhibition of amiloride-sensitive pathways (mostly Na channels). * $P < 0.05$ vs. control values in normoxia. Modified from Vivona et al. (111).

nasal potential measurements (71), but not Na reabsorption by alveolar epithelium, it is unclear to what extent this parameter is predictive of altered alveolar Na transport. Nevertheless, experimental evidence in support of this hypothesis comes from genetically engineered mice partially deficient in the apical (alveolar facing) epithelial sodium channel, which show greater accumulation of lung water in hypoxia (94) and hyperoxia (33).

It is important to note that, during ascent, the rate of filtration into the interstitial space and the alveoli increases slowly as PAP increases with exercise and increasing degree of hypoxia. Genetically or constitutionally reduced alveolar Na transport capacity in combination with hypoxic inhibition of Na transport might blunt the removal of alveolar fluid, causing greater fluid accumulation and hypoxemia. In contrast, a high capacity of alveolar Na transport, with or without pharmacological stimulation, might limit alveolar flooding (51). It is obvious, however, that reabsorption can only be effective when the alveolar barrier is greatly intact and the rate of fluid transudation is modest so that the rate of reabsorption can be higher

than leakage, a prerequisite not granted in situations when microvascular pressures are high and proteins and erythrocytes escape easily into the alveolar space (105).

Because HAPE can be fully prevented by decreasing PAP, more specific drugs that solely target alveolar epithelial Na and water reabsorption are required to establish, on a quantitative basis, the role of active alveolar fluid reabsorption in the pathophysiology of HAPE.

Inflammation. It is conceivable that the pressure required for transvascular leakage decreases when the integrity of the alveolar capillary barrier is weakened. Thus any inflammatory process of the respiratory tract that extends to the alveolar space would facilitate edema formation at lower capillary pressures. Indeed, increased fluid accumulation during hypoxic exposure after priming by endotoxin or viruses in animals (23) and the association of previous viral infections (predominantly of the upper respiratory tract) with HAPE in children (31) support this concept. Under conditions of increased permeability, HAPE may also occur in individuals with normal hypoxic pulmonary vascular response or in susceptible individuals at lower altitudes around 2,000 m (35).

Reduction in cross-sectional area of the pulmonary capillaries. Any reduction in the capillary bed should enhance edema formation because of reduced reserve capacity and thus higher resistance to increased flow. Examples are pulmonary edema at low altitude after pulmonary embolism in nonoccluded lung areas (58). Minor, unrecognized pulmonary embolism may explain a HAPE-like presentation at moderate altitudes (35) or unexpected HAPE in nonsusceptible individuals at high altitude (P. Bärtsch, E. Grünig, and E. Mayer, unpublished observations). Furthermore, unilateral absence of a main pulmonary artery is a known factor for HAPE at altitudes around 2,000 m (39).

PHYSIOLOGICAL ASPECTS OF HAPE AND QUESTIONS FOR FURTHER RESEARCH

HAPE is now well established as the consequence of hypoxic pulmonary vasoconstriction (HPV) and sufficient transmission of high PAP and blood flow to portions of the pulmonary capillary bed, most likely due to regional unevenness in HPV. Although strong HPV is a characteristic shared by most individuals who develop HAPE, there probably can be no absolute resistance to HAPE, even in "nonsusceptible" individuals if altitude gained and ascent rate are high enough. HPV is thought to be an adaptive physiological mechanism that serves two purposes. In utero, combined with a patent ductus arteriosus, it directs venous blood flow to the arterial circulation and away from the nonventilated non-gas-exchanging lung. After birth, it enhances ventilation-perfusion matching and, particularly with regional lung disease, it helps to preserve oxygenation of arterial blood by diverting blood flow away from poorly ventilated hypoxic areas. HPV, however, becomes detrimental when the whole lung or large portions of it are exposed to hypoxia, especially in those individuals who have a particularly vigorous HPV. Acute exposure predisposes them to HAPE and prolonged exposure to right heart overload, resulting in congestive right heart failure, a syndrome also called subacute mountain sickness. Invasive measurements of PAP in Tibetans, the population that is genetically best adapted to high altitude demonstrate that evolution has selected against

and virtually abolished HPV (37), possibly by a greater production of NO (19). These findings suggest that HPV has no vital significance even in utero and that it reduces the high-altitude tolerance of populations living at low altitude.

The fluid leak in humans with HAPE (and in animal models) supports the concept proposed by West et al. (115) that increased pulmonary capillary pressure can lead to a permeability-type edema in the absence of inflammation and challenges the classical paradigm that hydrostatic stress can only lead to ultrafiltration of protein-poor fluid. The same pathophysiology of capillary leak at high pressure and flow (overperfusion edema) exceeding local mechanisms of fluid absorption and clearance that is central to HAPE is also relevant to other forms of pulmonary edema at low altitude, including maximal exercise in highly trained humans or horses, pulmonary embolism, reperfusion lung injuries (thromboendarterectomy and acute graft dysfunction of the new transplanted lung), and neurogenic pulmonary edema. The study of HAPE has taught us much about the physiology of the lung and pulmonary vasculature, and it is hoped that successful strategies for HAPE prevention and treatment may find broader clinical application in pulmonary edema of other etiologies.

Despite considerable recent advances in our understanding of the mechanisms that account for HAPE, there remain many hypotheses to be challenged or questions to be answered, such as the relation between susceptibility to HAPE and subacute mountain sickness, the remodeling of the pulmonary circulation in newcomers to high altitude, or the genetic basis of susceptibility. We need to examine the significance of fluid clearance from the alveoli for the pathogenesis of HAPE, ideally with drugs that have no other actions except stimulation of sodium reabsorption, to more fully characterize the leak of the alveolocapillary barrier and to elucidate the mechanisms by which dexamethasone prevents HAPE, including whether inhaled glucocorticoids may be sufficient.

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