Physiological aspects of high-altitude pulmonary edema

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Bärtsch, Peter, Heimo Mairbäurl, Marco Maggiorini, and Erik R. Swenson. Physiological aspects of high-altitude pulmonary edema. J Appl Physiol 98:1101–1110, 2005; doi:10.1152/japplphysiol.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.

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
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.](image-url)
HPV at a constant alveolar PO2 (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 recuitability 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 with hypoxia (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-susceptible 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...
Invited Review

PHYSIOLOGICAL ASPECTS OF HAPE

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).

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).

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

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<tr>
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<th>550 m</th>
<th>4,559 m</th>
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<tr>
<td></td>
<td>Con (n = 8)</td>
<td>HAPE-S (n = 9)</td>
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<tr>
<td>White blood cell count, 10³/ml</td>
<td>8.1 ± 6.3</td>
<td>9.5 ± 8.1</td>
</tr>
<tr>
<td>Macrophages, %</td>
<td>94 ± 95</td>
<td>83 ± 82</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>1 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Red blood cells, %</td>
<td>1 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>of total BAL cells</td>
<td>1 ± 4</td>
<td>6 ± 51*</td>
</tr>
<tr>
<td>Total protein, mg/dl</td>
<td>1 ± 2</td>
<td>14 ± 34</td>
</tr>
<tr>
<td>Total protein, % of plasma protein</td>
<td>1 ± 3</td>
<td>20 ± 48</td>
</tr>
<tr>
<td>PAP systolic, mmHg</td>
<td>22 ± 26</td>
<td>37*</td>
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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).
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 fibrinopeptide A and D-dimer in BAL fluid (105) in early HAPE indicate that hydrostatic stress can only lead to ultrafiltration of protein-poor fluid, 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 β2-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 β2-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
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. Grüning, 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 arteriosis, 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

**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 Na⁺-K⁺-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).
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 (thromboendoarterectomy 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 altitude. 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.

REFERENCES


