

Chapter 61

High-Altitude Pulmonary Edema

Erik R. Swenson

Abstract High-altitude pulmonary edema (HAPE) is an uncommon form of pulmonary edema that occurs in healthy individuals within a few days of arrival at altitudes above 2,500–3,000 m. The crucial pathophysiology is an excessive hypoxia-mediated rise in pulmonary vascular resistance (PVR) or hypoxic pulmonary vasoconstriction (HPV) leading to increased microvascular hydrostatic pressures despite normal left atrial pressure. The resultant hydrostatic stress can cause both dynamic changes in the permeability of the alveolar capillary barrier and mechanical damage leading to leakage of large proteins and erythrocytes into the alveolar space in the absence of inflammation. Bronchoalveolar lavage (BAL) and pulmonary artery (PA) and microvascular pressure measurements in humans confirm that high capillary pressure induces a high-permeability non-inflammatory-type lung edema; a concept termed “capillary stress failure.” Measurements of endothelin and nitric oxide (NO) in exhaled air, NO metabolites in BAL fluid, and NO-dependent endothelial function in the systemic circulation all point to reduced NO availability and increased endothelin in hypoxia as a major cause of the excessive hypoxic PA pressure rise in HAPE-susceptible individuals. Other hypoxia-dependent differences in ventilatory control, sympathetic nervous system activation, endothelial function, and alveolar epithelial sodium and water reabsorption likely contribute additionally to the phenotype of HAPE susceptibility. Recent studies using magnetic resonance imaging in humans strongly suggest nonuniform regional hypoxic arteriolar vasoconstriction as an explanation for how HPV occurring predominantly at the arteriolar level can cause leakage. This compelling but not yet fully proven mechanism predicts that in areas of high blood flow due to lesser vasoconstriction edema will develop owing to pressures that exceed the structural and dynamic capacity of the alveolar capillary barrier to maintain normal

alveolar fluid balance. Numerous strategies aimed at lowering HPV and possibly enhancing active alveolar fluid reabsorption are effective in preventing and treating HAPE. Much has been learned about HAPE in the past four decades such that what was once a mysterious alpine malady is now a well-characterized and preventable lung disease. This chapter will relate the history, pathophysiology, and treatment of HAPE, using it not only to illuminate the condition, but also for the broader lessons it offers in understanding pulmonary vascular regulation and lung fluid balance.

Keywords High altitude pulmonary edema • Hypoxia • Alveolar fluid balance • Alveolar capillary barrier • Microvascular hydrostatic pressure • Capillary stress failure

1 Introduction

High-altitude pulmonary edema (HAPE) is an uncommon form of pulmonary edema that occurs in healthy individuals within a few days of arrival at altitudes above 2,500–3,000 m. It can be life-threatening, but with recognition, descent, and/or treatment complete recovery is the rule. Indeed, a previous bout of HAPE does not preclude future successful ascents to even higher altitudes or sojourns in the mountains, especially if the rate of ascent is slowed allowing for acclimatization. Effective drug prophylaxis of HAPE and treatment are possible if slow ascent rates are not feasible and descent is not possible. The crucial pathophysiology is an excessive hypoxia-mediated rise in pulmonary vascular resistance (PVR) or hypoxic pulmonary vasoconstriction (HPV) leading to increased microvascular hydrostatic pressures despite normal left atrial pressure. The resultant hydrostatic stress can cause both dynamic changes in the permeability of the alveolar capillary barrier and mechanical damage leading to leakage of large proteins and erythrocytes into the alveolar space in the absence of inflammation. Bronchoalveolar lavage (BAL) and pulmonary artery (PA) and microvascular pressure measurements in humans confirm that high capillary pressure induces a high-permeability non-inflammatory-type

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lung edema; a concept termed “capillary stress failure.” Measurements of endothelin and nitric oxide (NO) in exhaled air, NO metabolites in BAL fluid, and NO-dependent endothelial function in the systemic circulation all point to reduced NO availability and increased endothelin in hypoxia as a major cause of the excessive hypoxic PA pressure rise in HAPE-susceptible individuals. Other hypoxia-dependent differences in ventilatory control, sympathetic nervous system activation, endothelial function, and alveolar epithelial sodium and water reabsorption likely contribute additionally to the phenotype of HAPE susceptibility. Recent studies using magnetic resonance imaging in humans strongly suggest nonuniform regional hypoxic arteriolar vasoconstriction as an explanation for how HPV occurring predominantly at the arteriolar level can cause leakage. This compelling but not yet fully proven mechanism predicts that in areas of high blood flow due to lesser vasoconstriction edema will develop owing to pressures that exceed the structural and dynamic capacity of the alveolar capillary barrier to maintain normal alveolar fluid balance. Numerous strategies aimed at lowering HPV and possibly enhancing active alveolar fluid reabsorption are effective in preventing and treating HAPE.

Much has been learned about HAPE in the past four decades such that what was once a mysterious alpine malady is now a well-characterized and preventable lung disease. This chapter will relate the history, pathophysiology, and treatment of HAPE, using it not only to illuminate the condition, but also for the broader lessons it offers in understanding pulmonary vascular regulation and lung fluid balance.

2 Clinical Presentation

2.1 Epidemiology

Two distinct populations are affected by HAPE. The first involves well-acclimatized high-altitude residents returning from low-altitude stays (re-entry HAPE) and the second involves rapid ascent of unacclimatized lowlanders. Although good clinical descriptions of HAPE date back over 100 years, it was variably diagnosed as bronchitis, pneumonia, or heart failure. The first medical description of HAPE as a distinct entity was recognized in Peru as re-entry HAPE [1]. The first cases of HAPE in unacclimatized lowlanders going to high altitude were reported from the Rocky Mountains [2]. Most likely, both forms share the same pathophysiology; that of a pulmonary vasculature and lung parenchyma ill prepared to handle a sudden rise in vascular resistance induced by a low inspired partial pressure of oxygen, but most of our knowledge has been gained in studying lowlanders. Altitude, ascent rate, and, importantly, individual susceptibility are the major determinants of HAPE in mountaineers and trekkers and in

those with re-entry HAPE. The prevalence of HAPE ranges from less than 0.2% in a general mountaineering population when climbing in 3 days or more to altitudes between 4,000 and 5,000 m to 7% if the same altitudes are reached within 1 day. A similar increase in HAPE incidence of 2.5 versus 15.5% occurs when an altitude of 5,500 m is reached by airlift as opposed to trekking over 4–6 days. In those with a history of radiographically documented HAPE at 4,559 m, the likelihood of developing HAPE is 60% with a 1–2-day ascent to the same altitude [3]. Much has been learned about the pathophysiology, treatment, and prevention of HAPE from studies of these individuals, who have generously and enthusiastically volunteered for a variety of investigations, often of an invasive nature in the laboratory and at high altitude. They have a variety of physiological characteristics and responses to hypoxia, which appear to be quite disadvantageous at high altitude, as discussed below.

Although HAPE is a risk in mountaineers it also occurs at lower altitudes between 2,500 and 3,000 m in the ski and mountain resorts of Asia, Europe, South America, and North America. The estimated incidence in visitors to the Colorado Rockies is 0.01–0.1% [3]. Women may be slightly less susceptible to HAPE than men [4]. Re-entry HAPE has been also reported from the Rocky Mountains and appears to run in susceptible families and affect predominantly children, findings similar to those reported from the Andes [5, 6]. Most recently, a case series of HAPE at altitudes between 1,400 and 2,400 m in ski resort areas with facilities for skiing up to 3,200 m [7] has been reported, but no incidence figures were given. Susceptibility for HAPE in the tourists may have been increased by preceding or unrecognized underlying illness as discussed later in this review, such as viral infections, pulmonary embolism, or diastolic heart dysfunction.

Subclinical or very mild HAPE likely occurs and causes either no problems or minimal symptoms that are ignored or attributed to other factors. The true incidence of subclinical HAPE is unknown, although several studies at altitudes between 4,000 and 5,000 m have suggested that as many as 50% of persons may have subclinical fluid accumulation in the lung consistent with occult edema that resolves spontaneously despite remaining at high altitude [8–11]. This incidence is as high as that for acute mountain sickness (AMS), which has been associated with mild gas exchange impairment [12, 13]. The incidence may be overestimated because these studies did not use chest radiographs, but rather used very indirect measures of lung water changes such as spirometry, closing volume, and/or transthoracic impedance, all of which can vary for other reasons related to the high-altitude environment, including intense exercise and increased cardiac output, cold/dry-air-induced mild bronchoconstriction, and hypocapnia [14]. Recently a high incidence of subclinical HAPE could not be confirmed at 4,559 m in a study of climbers using an array of pulmonary function measurements including body plethysmography, chest radiography, arterial blood

gases, and compliance measurements [15]. The same measurements made in a smaller group of subjects diagnosed with mild HAPE by detectable radiographic interstitial edema showed only very mild abnormalities, suggesting that many pulmonary function parameters may not be very sensitive to small changes in interstitial fluid volume.

2.2 Diagnosis and Evaluation

HAPE in lowlanders occurs within 2–5 days after arrival at high altitude [3]. It is rarely observed below altitudes of 2,500–3,000 m and after 1 week of acclimatization. In high-altitude residents retuning home after a stay at low altitude the onset is similar. In most cases, it is preceded by symptoms (headache, nausea, and lassitude) of AMS, which afflict upward of 50% of newcomers to high altitude. The clinical presentation of HAPE does not differ much from that of any other form of pulmonary edema as it evolves from its mild to its severe form. Early symptoms of HAPE include exertional dyspnea different from past experience at that altitude or in relation to that of one's companions, cough, chest tightness, and reduced exercise performance. As edema progresses, cough worsens, breathlessness is present at rest, and orthopnea develops. Gurgling in the chest and pink frothy sputum indicate advanced cases. The physical examination reveals cyanosis, tachypnea, tachycardia, and elevated body temperature generally not exceeding 38.5°C. Crackles are discrete at the onset, typically located over the middle lung fields. Often, auscultation underestimates the more widespread disease on the chest radiograph. In advanced cases, as arterial oxygen saturation plummets, signs of concomitant high-altitude cerebral edema such as ataxia and decreased consciousness are frequent findings and consequences.

There are no unequivocal characteristic diagnostic laboratory findings with HAPE [3]. Abnormal results may be due to accompanying dehydration, stress, and preceding exercise. Arterial blood gas and oxygen saturation measurements in advanced HAPE at 4,559 m demonstrate its severity; mean arterial PO_2 in the mid 20-mmHg range versus 40–45 mmHg in healthy controls, and arterial oxygen saturations below 50% versus 70–85% [3]. Chest radiographs and CT scans of early symptomatic HAPE show a patchy and sometimes peripheral distribution of edema. The radiographic appearance of advanced HAPE becomes more homogenous and diffuse [16, 17]. Surprisingly, in patients with two episodes of HAPE, the radiographic appearance is not always similar, suggesting that intrinsic structural vascular and parenchymal regional differences do not necessarily dictate where edema may first develop [17] except in the rare cases of unilateral absence of a PA, in which the edema always occurs in the contralateral lung receiving the entire cardiac output [18]. BAL findings show a protein-rich exudate and mild alveolar hemorrhage (Fig. 1)

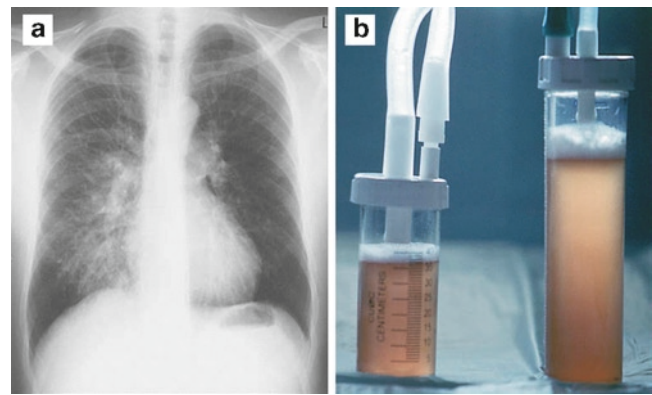


Fig. 1 Chest radiograph with bronchoalveolar lavage fluid aliquots (first and fifth) from a representative subject with early high-altitude pulmonary edema. The radiograph shows interstitial and alveolar infiltrates and the lavage performed after the X-ray was taken shows mild alveolar hemorrhage. (Reproduced from [20] with permission. Copyright 2002 American Medical Society. All rights reserved)

which initially is noninflammatory, but can progress to a more inflammatory picture as discussed below [19–21]. In all cases echocardiographic and PA catheterization studies at high altitude have always shown marked pulmonary hypertension. Autopsies reveal distended PAs with thrombi and infarction, diffuse bloodstained alveolar edema with bloody foamy fluid present in the airways, hyaline membranes, but little to no evidence of left ventricular failure or leukocytic infiltration [22].

3 Pathophysiology

Since the recognition of HAPE as a noncardiogenic pulmonary edema in the 1960s, a number of pathophysiological mechanisms have been postulated to explain the sudden appearance of pulmonary edema in otherwise young, healthy, and physically fit individuals. From the first modern descriptions it was clear that pulmonary hypertension and HAPE were inextricably linked, suggesting a primary hemodynamic basis, but the story became more complicated with subsequent studies in both human and animals suggestive of an inflammatory pathogenesis. A final chapter in our understanding of HAPE is evolving with the growing appreciation that active alveolar epithelial sodium and water reabsorption, and its sensitivity to hypoxia, must now be taken into account, as is true for other forms of pulmonary edema [23].

3.1 Hemodynamics

Right-sided heart catheterization studies in untreated cases of HAPE at high altitude [24, 25] revealed mean PA pressures of 60 mmHg (range 35–115 mmHg), but normal PA wedge pressures. These pioneering studies were crucial in putting to

rest the idea that HAPE was acute left-sided heart failure at high altitude. Subsequently, less invasive estimations of systolic PA pressure by echocardiography have substantiated the catheterization data with values between 50 and 100 mmHg for subjects with HAPE and 30–50 mmHg for healthy controls [26, 27]. It is well established that excessive PA pressure precedes the development of HAPE and is not a consequence [26]. The critical role of high PA pressure is further confirmed by the fact that any intervention (descent, oxygen, or drugs) which lowers PA pressure can improve gas exchange in HAPE [27, 28] and in the case of drugs is effective for treatment [29] and prevention [26].

Individuals susceptible to HAPE, as mentioned already, have many physiological characteristics (Table 1) that place them at risk for high-altitude problems. The most important among these is a strong HPV response. Although they have resting PA pressures within the normal range at low altitude, their exaggerated PA pressure responses with exercise and even during sleep in normoxia [30–32] point to a constitutional hyperreactivity of the pulmonary circulation to stress (Fig. 2). Studies in relatives of HAPE-susceptible individuals have not been undertaken as yet, but in a recent study of young children and their fathers at high altitude (3,450 m) it was shown that the increase in PA pressure from low to high altitude of each child correlated with that in the father [33], suggesting that HPV is in part genetically determined, as already established for the hypoxic ventilatory response [34].

Recently, right-sided heart catheterization studies by Maggiorini et al. [35] using the single occlusion technique at the Capanna Margherita in the Swiss–Italian Alps (4,559 m) in controls and HAPE-susceptible climbers showed that the exaggerated rise in PA pressure in individuals susceptible to HAPE is accompanied by increased microvascular (vessels less than 100 μm in diameter) pressure above 20 mmHg in those developing HAPE (Fig. 3). This threshold value accords with experimental observations in dogs of a PO_2 -independent critical microvascular pressure of 17–24 mmHg, at which the lungs continuously leak fluid and gain weight [36]. These results suggest that increased microvascular pressures with

pulmonary arterial hypertension rather than upstream arterial pressure elevation itself are the crucial hemodynamic factor in the pathophysiology of HAPE, since as this study showed some susceptible subjects with equivalently high PA pressures but lower microvascular pressures did not develop clinical or radiological evidence of edema.

The basis for high hypoxic PA pressures in HAPE-susceptible subjects is not fully known and likely is multifactorial. PVR is the sum of many influences including those intrinsic to the vascular smooth muscle, but also those related to vascular endothelium, lung volume, ventilatory control, left ventricular end-diastolic pressure, and neurohumoral responses. As noted in Table 1, HAPE-susceptible subjects have lower hypoxic ventilatory responsiveness (HVR) (set largely by the peripheral chemoreceptors) [37–39], which results in a lower alveolar PO_2 at the same altitude (or F_iO_2) than in a HAPE-resistant subject, and thus a stronger stimulus for HPV. In addition to a lower alveolar PO_2 , a lower HVR may lead to a smaller fall in alveolar PCO_2 and less hypocapnic inhibition of HPV [40]. To what extent the greater HPV of HAPE-susceptible subjects is due to lower HVR has never been established by testing HAPE-susceptible and HAPE-resistant control subjects over a range of inspired PO_2 , so that the influence of differences in HVR can be eliminated by comparing the two groups at equivalent alveolar PO_2 s (the predominant stimulus of HPV) and arterial oxygen saturation. Animal studies have revealed that HVR and HPV may be linked in two other ways. The first is the influence of arterial PO_2 itself because the bronchial arterial circulation perfuses the vaso vasorum of the pulmonary vasculature. Isolated perfusion of the bronchial artery in sheep with deoxygenated blood, when alveolar PO_2 and systemic PO_2 are held constant, increases PA pressure [41]. The second is via the peripheral

Table 1 HAPE-susceptibility characteristics

Hemodynamic

- Exaggerated hypoxic pulmonary vasoconstriction (HPV)
- Greater normoxic exercise-induced PA pressure elevation
- Augmented sympathetic tone with hypoxia
- Reduced vascular endothelial nitric oxide production
- Increased vascular endothelial endothelin production

Pulmonary

- Smaller lung volumes
- Reduced recruitment of diffusing capacity with hypoxia and exercise
- Possibly reduced alveolar epithelial $\text{Na}^+/\text{H}_2\text{O}$ reabsorptive capacity

Ventilatory and Renal

- Lower hypoxic ventilatory responsiveness (HVR)
- Possibly reduced natriuretic response to acute hypoxia

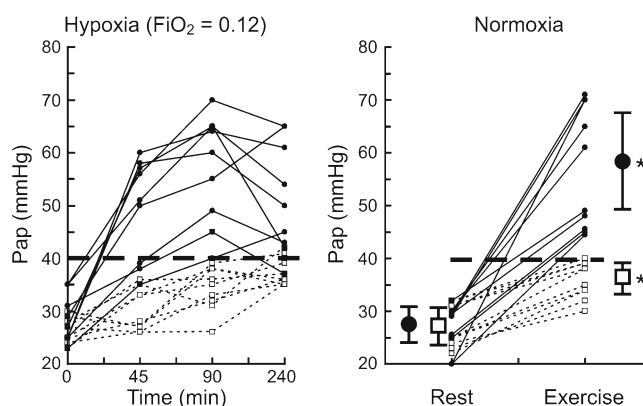


Fig. 2 Pulmonary artery pressure (PAP) in high-altitude pulmonary edema (HAPE)-susceptible (HAPE-s) individuals (continuous lines and filled symbols) and in nonsusceptible controls (dashed lines and open symbols) during exposure to normobaric hypoxia (left) and before and during exercise on a bicycle ergometer (right). The highest PAP recordings during exercise (75–150 W) are shown. (Reprinted from [32] with permission from Elsevier)

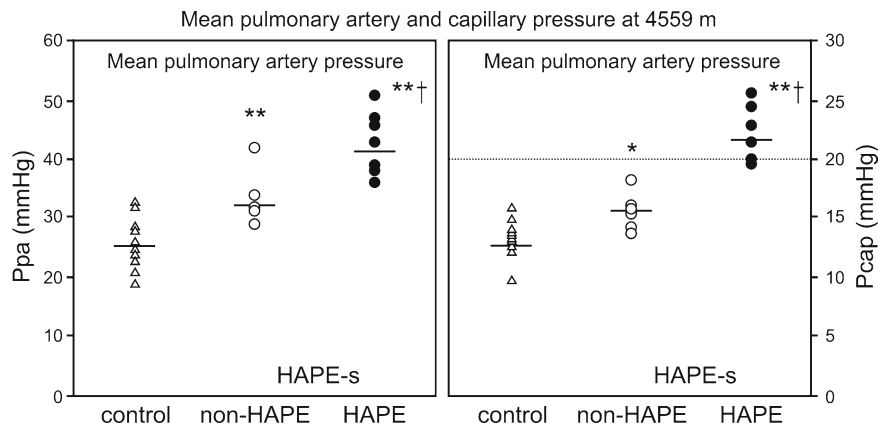


Fig. 3 Mean PAP (P_{pa}) and pulmonary capillary pressure (P_{cap}) in 14 controls and in 16 HAPE-s subjects at high altitude. HAPE-s is further divided into those who developed HAPE ($HAPE$) and those who did not develop

HAPE ($non-HAPE$). Bars indicate the mean values in each group. * $p < 0.05$, ** $p < 0.01$ versus control, † $p < 0.01$ versus non-HAPE. (Reproduced from [35] with permission from Lippincott Williams & Wilkins)

chemoreceptors independent of the alveolar PO_2 . In anesthetized animals with fixed minute ventilation, vagotomy of the lungs [42] or manipulation of the carotid body [43], both of which alter a neural afferent–efferent pathway, results in greater HPV for an equivalent alveolar PO_2 . These findings suggest that the peripheral chemoreceptors when stimulated help to blunt HPV by two mechanisms: by increasing ventilation to reduce the stimulus itself and by diminishing the vascular responsiveness to that stimulus. There is another peripheral chemoreceptor-mediated response to hypoxia that may have relevance in HAPE susceptibility. In animal and human studies, acute hypoxia of moderate intensity ($F_{I}O_2$ of 0.12–0.14) causes diuresis and natriuresis; this in humans is greater in those with higher HVR [44]. Because HAPE-susceptible subjects have low HVR, they may be disadvantaged by a limited hypoxic diuretic response as suggested by a field study in which several HAPE-susceptible subjects had no diuresis in contrast to HAPE-resistant subjects [45], in part by greater activation of the renin–angiotensin system [46, 47] and higher sympathetic activity [48], but also less chemoreceptor-mediated natriuresis.

Increased sympathetic tone may also contribute to stronger HPV. Microneurography in HAPE-susceptible subjects demonstrates increased skeletal muscle sympathetic tone during hypoxia at low altitude and prior to HAPE at high altitude [47], although this study, similar to the HPV studies, suffers from a lack of control on the strength of the hypoxic stimulus due to differences in HVR. In accordance with these findings, increased plasma and/or urinary levels of norepinephrine compared with the levels for controls precede and accompany HAPE [48]. Some studies in adult animals and man have found that stimulation of the sympathetic innervation of the lung augments HPV [49] via α -receptor stimulation [50] and that it is reduced it with autonomic blockade [51, 52]. In an in vivo canine model of isolated cerebral hypoxia by selective perfusion of the brain with hypoxic

venous blood, there was intense sympathetic activation, increased PA pressure, and considerable pulmonary edema [53]. Thus, it is conceivable that increased hypoxia-mediated sympathetic activity contributes to brisk HPV and HAPE development and α -adrenergic antagonists may be useful [28]. The importance of heightened sympathetic-mediated pulmonary hypertension is well established in neurogenic pulmonary edema [54], an acute pulmonary edema that may share similarities with HAPE.

A difference in lung volumes is a very consistent finding in studies of lung function in HAPE-susceptible and HAPE-resistant subjects. HAPE-susceptible individuals have 10–15% lower total lung capacity (TLC) and vital capacity than HAPE-resistant controls [39, 55–57] and in the only study to measure functional residual capacity (FRC) a 30% lower value was found [56]. The possible greater importance of differences in FRC than in the maximal lung volumes is that FRC is the operating lung volume around which normal breathing and perfusion occurs and itself is a determinant of PVR. Studies in isolated dog lungs have shown that PVR is minimal at 50% of TLC and rises greatly with a fall in volume [58]. Interestingly, the HAPE-resistant subjects had a FRC-to-TLC ratio of 0.52, whereas the ratio was 0.42 in the HAPE-susceptible group [56]. HAPE-susceptible subjects show greater steady-state arterial desaturation in the supine position than HAPE-resistant individuals at a simulated altitude of 4,000 m that resolves with 2 min of stimulated breathing [57], indicative of a lower FRC close to the point of airway closure in dependent lung regions typically seen when breathing at lower lung volumes. Pointing to a slight but potentially important restrictive defect is the higher ratio of the forced expiratory volume in 1 s to the forced vital capacity in HAPE-susceptible subjects and their associated reduced maximal diffusing capacity [56] that indicate a smaller capillary bed and less vascular recruitability. Because of their lower lung volumes, HAPE-susceptible subjects may need to

recruit a larger fraction of their total alveolar surface area as they breathe and thus subject their lungs to greater stretch. In vitro studies have shown that alveolar epithelial permeability increases with both greater frequency and peak stretch magnitude [59]. It must be noted that lacking any pre-HAPE lung function measurements and longitudinal follow-up data, one cannot distinguish whether HAPE-susceptible persons have an intrinsically different lung structure or whether an episode of HAPE heals with a small loss in lung volume and capillary bed, leading to an apparent slight restrictive defect.

In addition to the aforementioned extrinsic influences on the pulmonary vasculature, growing evidence points to possible differences of the vasculature itself. Presently, we lack any evidence for or against differences in vascular smooth muscle responsiveness to hypoxia, since studies in isolated smooth muscle from such subjects and controls have never been performed. The intrinsic responsiveness of the pulmonary vascular endothelium to hypoxia may likely be greater in HAPE-susceptible subjects; however, again owing to the problems arising from differences in HVR in awake and spontaneously breathing subjects, the true magnitude of pulmonary endothelial response differences may be overestimated. Nonetheless, compelling evidence is accumulating that the susceptibility to HAPE resides at the level of the vascular endothelium.

NO and endothelin 1 (ET-1) are important endothelial-derived vasodilator and vasoconstrictor mediators, respectively, in the pulmonary circulation and have received considerable attention in many forms of pulmonary hypertension. Lung NO production is reduced in HAPE-susceptible individuals, since they have lower exhaled NO concentrations during acute [60] and prolonged [61] exposure to hypoxia (Fig. 4) than HAPE-resistant individuals, and they have lower concentrations of the NO metabolites nitrate and

nitrite in BAL fluid [20]. Such measurements of lung NO metabolism do not perfectly reflect vascular production differences because NO is produced both by the vascular endothelium and by the alveolar and bronchial epithelia [62]. It is very likely that both vascular and bronchial sources of bioactive NO contribute to low pulmonary vascular tone and reduced HPV [62–64]. To better and more directly investigate the role of vascular endothelial NO differences, Berger et al. [65] assessed plasma nitrite concentration and showed that systemic vascular endothelial NO generation is reduced more in hypoxic HAPE-susceptible subjects than in controls within 90 min of hypoxic exposure and as a possible consequence there is less endothelial-dependent vasodilation to acetylcholine in hypoxia. Likely this is the case for the pulmonary circulation as the above-cited measurements of exhaled NO and metabolites of NO in BAL fluid suggest, however this has not been formally tested, or that of bronchial NO production. Tibetans, the population best adapted to high altitude, interestingly have greater pulmonary NO production than lowlanders and have minimal HPV [66]. The observation that inhaled NO fails to normalize PA pressure in hypoxic HAPE-susceptible individuals, in contrast to those resistant to HAPE [67], indicates impaired NO synthesis cannot fully account for the excessive pulmonary vascular reactivity in HAPE-prone subjects.

Circulating ET-1 concentrations are elevated almost three-fold at high altitude after 1–2 days and to a greater degree in HAPE-susceptible subjects [65, 68–70] and correlate with the rise in PA pressure. However, when ET-1 concentrations are measured with more acute hypoxia ranging from 5 to 90 min, there is no change at 5 min, when HPV is already evident, in either control or HAPE-susceptible subjects [71] and there is an equal rise of roughly 50% at 90 min in the two groups [65]. In humans, ET-1 infusion sufficient to raise

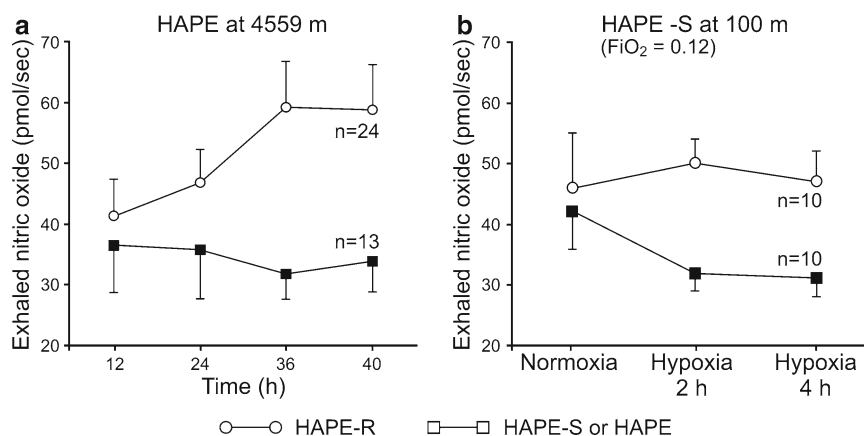


Fig. 4 (a) Exhaled NO after 40 h at 4,559 m in individuals developing HAPE (left) and in individuals not developing HAPE (HAPE-R) despite identical exposure to high altitude. (b) Exhaled NO in individuals with susceptibility (HAPE-S) and without

susceptibility (HAPE-R) to HAPE after 4 h of exposure to hypoxia (FIO₂=0.12) at low altitude (elevation 100 m). (a) Reproduced from [61] with permission; (b) reproduced from [60] with permission)

circulating concentrations tenfold has no effect on HPV after 2 h [72]. These data suggest that the early immediate rise in PA pressure with hypoxia may not be related to changes in circulating ET-1 levels, but that with longer hypoxic duration differences in ET-1 synthesis and/or clearance may become more important. When HAPE-susceptible subjects and HAPE-resistant subjects were studied, no important differences in either endothelial-derived vasodilator (prostacyclin and/or prostaglandin E) or vasoconstrictor (thromboxane A₂ and/or prostaglandin F_{2α}) prostaglandins and atrial natriuretic peptide were found with hypoxia of 30-min duration [30]. Longer periods of hypoxia or high-altitude sojourns have not been studied, despite the major role of these endogenous pulmonary vasoactive mediators in other forms of pulmonary hypertension. Other potential circulating pulmonary vasodilators and vasoconstrictors such as brain natriuretic peptide, adrenomedullin, and epoxyeicosatrienoic acids have not been studied, nor have differences in PA smooth muscle ion transporters or calcium signaling or responsiveness.

The heightened responsiveness of the pulmonary circulation in HAPE-susceptible persons raises several intriguing questions. What is the incidence of this in the general population? A tentative answer may be 9–10% as recently shown in a random group of 86 young healthy subjects that served as a control group in a study of primary pulmonary hypertension (PPH) [73]. Is this behavior a “*forme frusta*” of PPH and thus a risk for these individuals later in life to develop fixed PA hypertension with other pulmonary vascular stresses? Only prospective studies will provide the answer. Preliminary studies have ruled out differences in bone morphogenic protein receptor II, a leading candidate for familial PPH and some cases of sporadic PPH [74]. Clinically serious pulmonary hypertension does develop in a small but significant fraction of patients with sleep apnea, left ventricular failure, and chronic hypoxic lung disease [75], although why it occurs in some and not others with equally severe disease remains a mystery. Perhaps these individuals constitute the unknown percentage of persons with pulmonary vascular hyperreactivity, which in their earlier and healthier lives at low altitude never caused problems.

Since capillary pressure is elevated and likely the important site of excessive pressure in HAPE (Fig. 2), the question arises how hypoxic constriction of arterioles leads to edema. Three mechanisms have been suggested: transarteriolar leakage, irregular regional vasoconstriction with overperfusion in certain areas, and hypoxic venoconstriction. The evidence in hypoxic animals from the double occlusion technique [76, 77] reveals that the small arterioles are exposed to high pressure and that they are a site of transvascular leakage in the presence of markedly increased PA pressure in hypoxia [78]. Recently Parker et al. [79] showed that pulmonary microvascular endothelial cells grown in culture have a

20-fold lower hydraulic conductance than macrovascular arterial endothelial cells.

Pulmonary veins also constrict in response to hypoxia [80], thus increasing the resistance downstream of the fluid filtration region. Both mechanisms, alone or in combination, may contribute to edema formation; however, they cannot explain the patchy radiographic appearance of early HAPE as it appears on chest radiographs or CT scans, unless one postulates, in addition, that there is regional heterogeneity of hypoxic pulmonary arterial vasoconstriction.

If vasoconstriction in hypoxia is inhomogeneous, HAPE could be the consequence of uneven regional distribution of perfusion, with high flow in those areas with lesser vasoconstriction leading to increased microvascular pressure. The elevated microvascular pressures would be due to a longitudinal pressure drop across the upstream vessels insufficient to lower the tension below the threshold of 17–24 mmHg at the point of entry into the alveolar microvasculature [81], possibly aggravated further by increased venous resistance [36]. The concept of increased capillary pressure by a high blood flow was first postulated by Visscher [82] and was adapted to HAPE by Hultgren [83]. Recent investigations which demonstrate that HPV is uneven at rest provide substantial support to the concept of regional overperfusion in some areas. Intravascular microspheres used to map regional perfusion reveal that the spatial heterogeneity of the pulmonary perfusion in rats, pigs, and dogs increases with hypoxia [84]. This has now been corroborated in humans in studies using magnetic resonance imaging which found greater regional blood flow heterogeneity in hypoxic HAPE-susceptible individuals than in nonsusceptible controls [85, 86].

The basis of uneven regional HPV is not known, but may involve inhomogeneous localization of arterial smooth muscle, both in radial thickness and in distribution longitudinally along the arterial tree. As well, it may have its origin in intrinsic differences in local endothelial vasoactive mediator production or expression and heterogeneity of membrane ion channels and receptors involved in HPV, such as have been shown for endothelial-derived NO in the horse between dorsal and ventral lung regions [87]. If unevenness of regional HPV is responsible for HAPE, it would appear that it might decrease with time at altitude since slow ascent prevents HAPE even in susceptible individuals and HAPE rarely occurs after the first 5 days at a given altitude. One hypothesis accounting for these observations is that there may be rapid remodeling and generalized muscular hypertrophy of all pulmonary arterioles, which lead to a more even distribution of blood flow, but may also contribute to persistent excessive pulmonary hypertension and lead over some weeks to months to congestive right-sided heart failure termed “subacute mountain sickness” [88]. Although the idea that acute hypoxia-induced arteriolar muscularization and more

regional homogeneity in arteriolar resistance protects the microvasculature is attractive, it remains unproven and possibly refuted by recent data in children with pulmonary hypertension, who already have well-developed extensive PA smooth muscularization. These children are at considerable risk for HAPE with even slight gains in elevation [89]. What may be more important in acute acclimatization of the lung against the hydrostatic stress of high HPV is upregulated gene expression for collagen and other extracellular matrix proteins that help to strengthen the alveolar capillary barrier [90] as has been demonstrated in animal models of acute hypoxia and pulmonary vascular and parenchymal stress. Perhaps these changes in the parenchyma explain the smaller lung volumes noted earlier in HAPE-susceptible subjects.

In summary, these most recent investigations provide evidence for the concept of an overperfusion edema in HAPE occurring in some lung regions as a result of high blood flow under such large driving gradients that the increased microvascular and capillary pressures exceed the capacity of the alveolar barrier to maintain a fluid-free air space. The final piece in the puzzle will be to show with a single imaging modality capable of resolving flow and change in extravascular fluid that it is indeed these areas of high flow that do leak. The relevance of overperfusion injury extends to other clinically encountered forms of pulmonary edema, including alveolar fluid accumulation in nonoccluded areas in pulmonary embolism [91], following pulmonary thromboendarterectomy [92] and lung transplantation [93], and in the pulmonary edema during vigorous exercise and high cardiac outputs in highly trained athletes [94] or racehorses [95]. Increasing cardiac output manyfold over the baseline level with exercise will contribute to edema formation by increasing capillary pressure in overperfused areas owing to the rise in PA pressure as well as some further increase in the regional heterogeneity of blood flow [96]. Furthermore, it has been postulated that the greater increase of PA pressure in HAPE-susceptible individuals may slightly impair left ventricular filling because of leftward ventricular septal shift [97] and possible mild left ventricular stiffness [97] arising from decreased cardiac lymph clearance to the right side of the heart [98]. Mild diastolic dysfunction due to pulmonary hypertension could explain the significantly greater wedge pressure increase in HAPE-susceptible individuals compared with nonsusceptible controls during exercise in hypoxia [31], whereas at rest wedge pressure is normal in untreated HAPE [24, 25, 35]. A more recent echocardiographic study in HAPE-susceptible subjects exercising at 4,559 m before and after vasodilator therapy, however, found no evidence for left ventricular diastolic dysfunction [99]. Nonetheless, in many cases of HAPE, particularly at lower elevations, exercise may be the essential component of the setting that leads to pulmonary edema.

3.2 Inflammation

The first measurements of alveolar lavage fluid in mountaineers with and without HAPE were performed on Mt. McKinley in Alaska by Schoene et al. [19] and were then followed up by studies in hospitalized patients with HAPE in Japan [100]. In these reports the onset of HAPE could not be established with certainty, but particularly in the Japanese studies, the duration of HAPE may have been greater than 3 days. In addition to the high protein concentrations and mild alveolar hemorrhage, some but not all patients had significant neutrophilia and elevations of the levels of proinflammatory cytokines and neutrophil chemotactic factors, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, and leukotriene B₄. These observations strongly suggested that inflammation might be a causal factor in HAPE, consistent with an altered permeability leading to protein and fluid leak. Support for the concept was further marshaled in studies of animals with viral priming [101] or endotoxin administration [102] showing increased lung edema with hypoxic exposure compared with controls and prevention of lung edema with corticosteroid pretreatment, a classic anti-inflammatory therapy [103]. These studies lacked either histological or lavage measurements to show the proposed inflammation. Gonzalez and Wood pursued the hypoxia-mediated inflammation paradigm in a series of studies in rats exposed to 10% oxygen for upward of 4 h and found in various systemic vascular beds (brain, skeletal muscle, and brain) that hypoxia stimulated leukocyte adhesion to capillaries and increased their permeability via increased levels of reactive oxygen species and depletion of endogenous NO [104]. The lung microvasculature was not studied to determine whether the same leukocyte–endothelial adherence and increased permeability was taking place in the pulmonary capillaries. Intriguingly, they determined that the systemic capillary changes were the result of mast cell degranulation triggered in some way by hypoxic alveolar macrophages, because the effect of systemic hypoxia could be abrogated by cromolyn pretreatment and/or more than 90% depletion of alveolar macrophages and was not linked to the level of hypoxia in the systemic vascular bed [105]. Numerous *in vitro* studies have established that very severe (and likely lethal *in vivo* hypoxia – 7–20 mmHg) can cause spontaneous release of many proinflammatory and chemotactic mediators by leukocytes (reviewed in [20]) and vascular endothelial cells. These findings taken together continued to sustain the idea that HAPE might have a critical inflammatory pathogenesis.

The findings, however, that not all cases of HAPE had evidence of inflammation in alveolar lavage fluid [19], and the lack of evidence of *in vivo* thrombin and fibrin formation except in very advanced HAPE [106], indicated that in humans inflammation is possibly a secondary response to alveolar–capillary barrier disruption or edema. Furthermore,

prospective studies provided no evidence that inflammation and increased systemic vascular permeability preceded HAPE [107]. BAL in HAPE-susceptible and HAPE-resistant climbers within 1 day after ascent to 4,559 m from low altitude showed mild alveolar hemorrhage and increased serum-derived protein concentrations in the air space (Table 2) both in subjects ill with HAPE at the time of bronchoscopy and in those who developed HAPE within the next 24 h [20]. In fact, fully supporting the central role of hemodynamics in HAPE, we demonstrated a very strong correlation between the magnitude of pulmonary hypertension by echocardiography and the degree of hemorrhage and protein level elevation in the alveolar space (Fig. 5). In contrast, there were no increases in the levels of alveolar macrophages, neutrophils, and proinflammatory mediators (TNF- α , IL-1, and IL-8) at high altitude early in course of HAPE, despite the very high PA pressures recorded in these subjects. The only cytokine whose level was elevated both in the circulation and in the alveolar space was IL-6 and its level was only elevated after

the onset of HAPE. For ethical and practical reasons we could not perform serial lavages to document the time course of secondary inflammation. Alveolar macrophages harvested from the lavage fluids at sea level and at high altitude showed no differences in TNF, IL-8, IL-6, and IL-1 production between the HAPE-resistant and HAPE-susceptible subjects when stimulated under normoxic or hypoxic conditions, before and after endotoxin stimulation [108]. Thus, with regard to the work of Gonzalez and Wood discussed above, if alveolar macrophages sense hypoxia and elicit systemic permeability changes, altered permeability does not appear to involve signaling by these cytokines.

In numerous studies of humans at high altitude, increases in circulating IL-6 concentration are observed [105, 109–111] and have been taken as prime facie evidence for an inflammatory effect of hypoxia that might be critical to HAPE development [109]. The problem with this idea is that exercising muscle releases IL-6 in proportion to the intensity and duration of work both in normoxia and in hypoxia and is

Table 2 Bronchoalveolar lavage (BAL) characteristics in early HAPE

	550 m		4,559 m		
	CONT (n=8)	HAPE-S (n=9)	CONT (n=6)	HAPE-S (pre-HAPE) (n=6)	HAPE-S (ill) (n=3)
Leukocyte count ($\times 10^3/\text{mL}$)	8.1	6.3	9.5	8.1	9.8
Macrophages (%)	94	95	83	82	85
Neutrophils (%)	1	0	0	1	1
Red cell count ($\times 10^3/\text{mL}$)	3	4	10	26*	623*
Total protein (mg/dL)	1.8	1.5	14*	34*	163*
Systolic PAP (mmHg)	22	26	37*	61*	81*

BAL at 550 m and on the second day at 4,559 m in eight control subjects (CONT) and in nine HAPE-susceptible subjects (HAPE-S), of whom three had pulmonary edema at the time of BAL. Of those six HAPE-S without pulmonary edema at the time of BAL (*pre-HAPE*), four developed HAPE within 18 h after BAL

* $p < 0.05$ versus 550 m

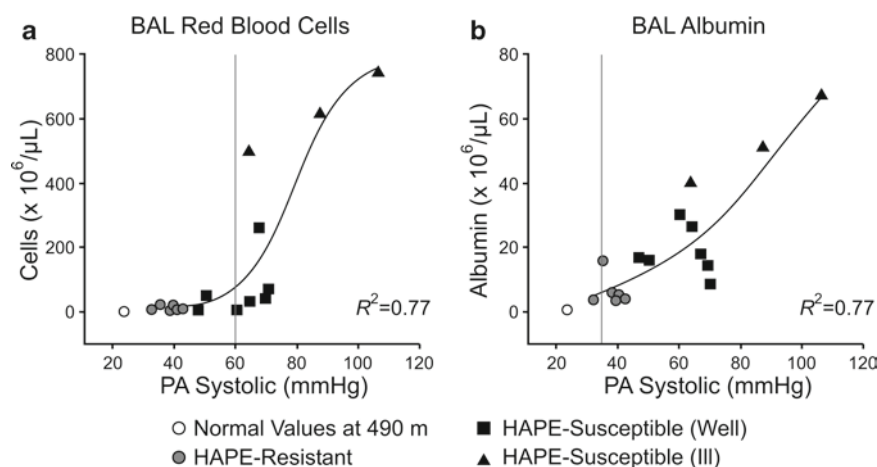


Fig. 5 Individual bronchoalveolar lavage (BAL) red blood cell count and albumin concentrations versus pulmonary artery systolic pressures at high altitude (4,559 m). The vertical lines denote a threshold systolic PAP (more than 60 mmHg) above which red blood cells (a) appear in the BAL fluid, in contrast to the lower pressure (35 mmHg) at which

albumin leakage occurs (b). The open circles at the lower left of (a) and (b) show the normal values for these at low altitude. The correlation coefficients are given for the best-fit curves of the values at high altitude ($p < 0.05$ for both curves). (Reproduced from [20] with permission. Copyright 2002 American Medical Society. All rights reserved)

driven to some extent by sympathetic nervous system activation with exertion [111, 112] and that with passive ascent to high altitude there is little to no increase in IL-6 concentration, even in HAPE-susceptible persons [113, 114]. Although IL-6 is considered a classic proinflammatory cytokine, there is considerable evidence that it may have equally important anti-inflammatory and endothelial permeability protective actions [112] and thus it might be equally plausible that IL-6 is released with severe hypoxia and after injury in the lung in an effort to limit inflammatory damage and capillary permeability. Studies in a recently developed IL-6 knockout mouse would be interesting in determining the role of IL-6 in high-altitude pathophysiology.

What initiates the secondary inflammation is not clear. It may be that sustained and increasing high pressures in untreated HAPE of sufficient duration can trigger inflammation [115] or the inflammation may represent part of the healing process of a markedly disrupted alveolar–capillary barrier that occurs in the severest cases of HAPE, especially with alveolar hemorrhage. Interestingly, it has been shown recently that heme and other breakdown products of red cell hemoglobin are chemotactic for neutrophils [116]. The surprise is that despite the intensity of apparent inflammation found in some subjects [100], the resolution of HAPE even at this stage is rapid and without apparent sequelae as opposed to the acute respiratory distress syndrome (ARDS), in which the concentration of alveolar neutrophilia and inflammatory cytokines is of magnitude equal to that seen in the later stages of HAPE [19, 100]. Despite overwhelming evidence against a primary inflammatory alteration of the alveolar–capillary barrier in HAPE, it is nevertheless conceivable that any concurrent process altering the permeability of the alveolar–capillary barrier will lower the pressure required for edema formation. Indeed, increased fluid accumulation during hypoxic exposure after priming by endotoxin or virus in animals [101, 102] and the association of preceding respiratory viral infections with HAPE in children [89, 117] support this concept. In conditions of increased permeability, HAPE may occur in individuals with more normal moderate hypoxic pulmonary vascular responsiveness. Thus, upper respiratory tract infections shortly before a sojourn in the mountains and vigorous exercise at altitudes between 2,000 and 3,000 m may explain in some cases why HAPE develops at a modestly low altitude [7].

3.3 Alveolar Fluid Clearance

Disruption of the alveolar capillary barrier and leak are the proximal cause of HAPE, but recent work in cell cultures and animal models has highlighted that alveolar fluid clearance mechanisms dependent upon active alveolar epithelial sodium and water reabsorption by both type II and type I

pneumocytes may contribute to the pathophysiology of HAPE. Active water and sodium transport from the alveolar space into the lung interstitium is important in normal lung fluid balance. Hypoxia decreases transepithelial sodium transport by reducing the expression and activity of the epithelial sodium channel (ENaC) and Na⁺/K⁺ ATPase proteins [118] in cultured alveolar epithelial cells possibly by an impairment of β_2 adrenergic receptor signaling [119]. In vivo hypoxia depresses fluid clearance from the alveoli of hypoxic rats and rabbits [120, 121]. Mice partially deficient in the ENaC develop greater accumulation of lung water in hypoxia [122] as well as in other forms of lung injury [123].

In an attempt to determine whether differences in active alveolar salt and water transport lead to HAPE susceptibility, Sartori et al. [124, 125] measured lower transepithelial nasal potentials in normoxia in HAPE-susceptible individuals than in nonsusceptible controls. The easily measured potential difference across the nasal mucosa is considered to be a good, but not perfect, surrogate for the alveolar epithelium. The reduced nasal potential difference in HAPE-susceptible individuals was attributed to lower sodium transport by the epithelial apical sodium channel (ENaC), pointing to a constitutional, possibly genetically, determined reduction of sodium transport across the respiratory epithelium. This has been questioned with a recent investigation that confirmed the difference in nasal potential between HAPE-susceptible individuals and controls in normoxia, but that found that this difference could not be attributed to differences in ENaC activity [126, 127], but rather to differences in chloride secretion, which contributes a large fraction of the potential difference in the nasal mucosa but not in the alveolar epithelium.

Another approach to study the relevance of alveolar transepithelial fluid reabsorption in HAPE has involved the use of β_2 -receptor agonists and glucocorticoids, both of which are known to upregulate ENaC and Na⁺/K⁺ ATPase (reviewed in [23]). Two recent field studies reported successful prevention of HAPE in HAPE-susceptible climbers with inhalation of salmeterol, a long-acting β_2 agonist [124] and orally administered dexamethasone [128] begun 1 day before ascent to 4,559 m. Owing to multiple actions of salmeterol and other β_2 adrenergic agonists, such as inhibition of HPV, increased HVR and ventilation, tightening of cell-to-cell contacts, and upregulation of NO production [129–131], the contribution of enhanced alveolar fluid clearance to the positive outcome of the study remains uncertain. Indeed, the protective effect of dexamethasone from a putative enhancement of alveolar fluid reabsorption could not be correlated to indirect measures of enhanced active alveolar sodium and fluid reabsorption (transepithelial nasal potential difference and expression of leukocyte messenger RNA for the sodium-transporting proteins), but rather to a surprising reduction of PA pressure at high altitude to be discussed below with respect to prevention of HAPE. Thus, what are needed are

selective and specific drugs to better evaluate the role of active alveolar fluid clearance in HAPE pathophysiology.

Interestingly, a putative link between virus infection and HAPE may rest in part upon infection-related downregulation of ENaC activity and diminished fluid clearance as recently shown in lungs of rats [132] infected with a nonreplicating influenza virus. In addition to the deleterious effect of reduced NO production in HAPE-susceptible subjects on PVR, NO may have a permissive and stimulatory effect on alveolar Na⁺ reabsorption as indirectly shown in rabbit lungs, which gain more weight at constant vascular pressure with inhibition of all nitric oxide synthase (NOS) activity [133] and more directly in cell culture studies showing depressed ENaC activity and fluid reabsorption in mice with loss of inducible NOS (iNOS), either by genetic knockout or by pharmacological inhibition [134]. In mice and man, a constitutive form of iNOS is the isoenzyme responsible for airway epithelial NO production [135].

ET-1 expression, as discussed earlier, increases with hypoxia, and plays a role in the elevated vascular pressures and lung water accumulation in HAPE. Two recent studies [136, 137] add another face to ET-1; that of inhibiting alveolar fluid clearance by activation of endothelial cell ET_B receptors. ET_B receptor binding by ET-1 generates NO, which as one of its effects includes downregulation of alveolar epithelial Na⁺/K⁺ ATPase by a non-cyclic GMP (GMP)-mediated mechanism [137]. The clinical importance of this possible effect of ET-1 on alveolar fluid clearance and HAPE awaits human studies with selective ET_B receptor antagonists, because two studies at high altitude with bosentan (a nonselective ET_A/ET_B receptor antagonist) have yielded conflicting results on PA pressure, exercise capacity, and gas exchange [70, 138].

4 Mechanisms of Increased Capillary Permeability

Although it is clear that microvascular pressures in HAPE are high, the reasons why the pulmonary vasculature leaks under high pressure are not completely resolved and remain an area of active investigation. Traditionally, pulmonary edema has been categorized as either noncardiogenic (increased permeability with exudative characteristics: high protein concentrations and markers of inflammation in the setting of normal or only modestly elevated intravascular pressures) or cardiogenic (elevated hydrostatic pressures leading to a noninflammatory protein-poor transudative leak). As alluded to already and discussed further later, BAL findings in nascent HAPE [20] reveal characteristics of a hydrostatic, but noncardiogenic noninflammatory edema suggesting pressure-induced alterations to the normal

permeability of the alveolar–capillary barrier or frank traumatic injury. This novel constellation of features in HAPE does not fit the conventional dichotomy of pulmonary edema, particularly in violating the dogma that high hydrostatic pressures alone should not lead to changes in microvascular permeability to high molecular weight substances.

4.1 Stress Failure

Early work by Fishman et al. [139] and amplified by Bachofen et al. [140] established that cardiogenic edema might, in fact, lead to alveolar protein accumulation. The concept was further advanced by West for HAPE (reviewed in [141]) after the publication of the first lavage findings in HAPE by Schoene et al. [19]. West et al. showed histological evidence obtained by electron microscopy for discrete ultrastructural disruptions in the alveolar capillary barrier in *in situ* perfused rabbit lungs with very high transmural pressures typical of severe HAPE, within cell membranes, between cells, and in the basement membranes of both the capillary endothelium and the alveolar epithelium, which could be responsible for the characteristic leak in HAPE. These changes, which they also showed in rats exposed to rapid simulated hypobaric “ascents” to 8,800 m [142], were termed “stress failure” of the pulmonary capillaries. They ascribed them to stretch and deformation of the extracellular collagen matrix in excess of its load-bearing capacity to maintain normal structural and permeability characteristics. Despite their traumatic-like appearance, even allowing red cell egress, these discontinuities can quickly close with reductions in pressure. Recently, it was proposed that hydrostatic disruptions of the alveolar–capillary barrier permit the leak of vascular endothelial growth factor (VEGF) from the alveolar air space (where it is in high concentration) to the capillary endothelium, where VEGF receptors are expressed and when activated promote vascular leakiness [143].

4.2 Dynamic Alterations in Permeability

Others have more recently suggested that the hydrostatic-induced permeability changes with hypoxia may have more than a mechanical basis. These may be dynamic noninjurious cellular responses because β adrenergic agonists [144] and gadolinium [145] reduce hydrostatic edema at constant vascular pressure. Perhaps dynamic changes in transcellular leakage via vesicle formation and fusion to create pathways that traverse the cell [146, 147] and paracellular pathways via alterations in gap junction assembly [148] arise from signals initiated when cells are deformed by pressure or stretch.

These responses may represent a pre-emptive attempt of the alveolar–capillary barrier to lower stress forces temporarily and prevent damage to the basement membranes as has been suggested in the systemic vasculature [149]. It is conceivable that these dynamic changes occur with moderate pressure elevations and precede the more profound “stress failure” changes observed in the studies by West et al. In the only study to examine *in vivo* permeability and histological disruptions, there was no correlation between the number of ultrastructural lesions and the extent of leak [150], suggesting that some of the permeability changes are not due to stress failure disruptions. Our lavage data at high altitude support this in showing a very mild protein leak even in HAPE-resistant subjects, in whom lavage protein concentrations were increased several-fold (Table 2) over those at low altitude [20]. Additionally, we found in nascent HAPE [20] that although there was considerable movement of serum-derived proteins into the air space, no equivalent air space to blood movement of two alveolar lining fluid proteins (surfactant protein A and Clara cell protein) was detectable. This unidirectional noninjurious selective leak is in marked contrast to the profound injury of the alveolar–capillary barrier in ARDS, in which air space proteins are detected in blood and reflect the severity of injury [151]. We did not measure VEGF back leak, but our findings with surfactant and Clara cell proteins do not support the idea [20] that VEGF is an amplifying factor. One, however, cannot rule out back leak of an alveolar space substance sufficient to interact with the endothelium but not to raise circulating levels. Studies with selective VEGF blockade are ultimately needed.

If hydrostatic forces persist, then gene upregulation and transcription of collagen and other extracellular matrix proteins are initiated to strengthen the alveolar–capillary barrier [90] and ultimately reduce stress failure and leak. These observations offer an explanation for the rapid recovery from HAPE and the protection from recurrence when reascending only several days after recovery from HAPE. The same changes in alveolar–capillary barrier strength occur in chronic heart failure and explain the lack of pulmonary edema in some patients despite chronically elevated pulmonary venous pressures, but at the price of mild restrictive changes and reduction in diffusing capacity.

5 Prevention and Treatment

5.1 Ascent Rates and Activity Level

Slow ascent is the most effective form of prevention even in susceptible individuals when the average daily ascent rate above 2,000 m does not exceed 350–400 m/day or with

staged ascent [3]. To avoid life-threatening illness, persons should not ascend further with any symptoms of altitude illness and should descend when mild symptoms do not improve after 1 day of rest. Because exercise-induced circulatory changes may enhance or cause pulmonary edema, vigorous exercise should be avoided during the first days of altitude exposure by individuals with a history of HAPE, and by those with symptoms of altitude illness or after a rapid ascent to altitudes above 3,500–4,000 m. As pointed out earlier, susceptibility to HAPE may be increased during and shortly after any infection.

5.2 Prediction of Susceptibility: Phenotypic and Genotypic Characteristics

Although as a group HAPE-susceptible individuals have a number of physiological characteristics and responses to hypoxia that arguably set them at risk (Table 1), these responses are not easily tested except in specialized laboratories. In a retrospective study, measurement of systolic PA pressure in hypoxia (2 h at an $F_{I}O_2$ of 0.12) identified HAPE-susceptible individuals with a specificity of 93% and a sensitivity 77% [152]. Measurements of lung volumes and HVR did not improve the identification. Given the low prevalence of HAPE between 0.2 and 15% (depending on the setting), such testing will always result in a considerable overestimation of HAPE-prone individuals. In fact, certain individuals with exaggerated acute HPV, perhaps as a result of perinatal hypoxia, do not develop HAPE in rapid ascents to 4,559 m [153]. Recently it was reported that subjects with a detectable patent foramen ovale (PFO) at sea level were at a four-fold greater risk for HAPE [154]. This study could not determine whether shunting across a PFO, which theoretically would act to unload the pulmonary circulation at the expense of greater arterial hypoxemia, was causative or simply a marker of susceptibility. If a PFO despite its potential to lower PA pressures by flow diversion were to predispose to HAPE, it could be explained by the greater stimulus of more arterial hypoxemia acting to enhance HPV by bronchial arterial hypoxemia [41] and greater sympathetic activation [49, 50, 53]. In the last analysis, general screening of trekkers or mountaineers for susceptibility to HAPE is not necessary, since this illness can clearly be avoided by slower ascent rates that permit adaptation of the pulmonary microvasculature to increasing pressures by remodeling [90].

Since accurate prediction of HAPE susceptibility by physiological characteristics has not been proven, there has been considerable interest in identifying a genetic marker(s) that might more readily serve the purpose. Numerous candidates have been sought on the basis of reported and hypothesized possible differences in vasoactive mediator production.

Although the pathogenesis of reduced NO production in HAPE susceptibility is unknown, a leading candidate is vascular endothelial NOS (eNOS). This has received some support in a Japanese and Asian Indian population [155] but these studies only found a weak segregation of eNOS polymorphisms between HAPE-resistant and HAPE-susceptible subjects, which was not borne out in an investigation of Caucasians with equal power [156]. Ethnic or environmental differences or different linkage disequilibrium in Asians and Caucasians could account for the differing results, or numerous other factors that determine eNOS activity and expression may be more important, such as differences in expression of caveolin 1 or the cationic amino acid transporter responsible for L-arginine uptake into endothelial cells. There is no association of HAPE susceptibility with the well-characterized angiotensin converting enzyme deletion polymorphism [157], which is associated with pulmonary hypertension in COPD [158] and in chronic high-altitude pulmonary hypertension [159]. Polymorphisms in the human VEGF gene were not found to be correlated to HAPE susceptibility [160]. Other gene polymorphisms, including those for the angiotensin receptor, aldosterone synthase, and serotonin transporter, have had very limited study [161]. Lastly, given the exciting results with dexamethasone prophylaxis described in the next section, it may be fruitful to explore whether HAPE susceptibility has any link to polymorphisms in the glucocorticoid receptor, which influence numerous aspects of cardiovascular and metabolic control [162].

5.3 Pharmacological Prophylaxis

The decision to use drug prophylaxis must be based upon an individual's past history at high altitude and a risk-benefit discussion of prophylaxis versus no prophylaxis. Nifedipine and other Ca^{2+} channel blockers that inhibit HPV are recommended for individuals with a history of unquestionable HAPE when slow ascent is not possible. Sixty milligrams daily of a slow-release formulation should be started with the ascent and end on the third to fourth day after arrival at the final altitude. Given the uncertainties mentioned already with regard to the preventive effect of high-dose inhaled β_2 -receptor agonists, nifedipine remains the drug of choice for HAPE prophylaxis.

Other drug prophylaxis options in animals and man have been recently studied. Not only do these other agents offer more flexibility and options, but also the surprising results obtained are providing new insights into HAPE pathophysiology and pulmonary vascular regulation. Interestingly, acetazolamide, long used for AMS prevention, blunts or abolishes HPV in animals and man at doses relevant to its clinical use [163, 164] and it was successful in an animal model of mild HAPE in reducing alveolar edema and hemorrhage

[165]. Studies in isolated PA smooth muscle cells suggest that acetazolamide prevents the increase in intracellular Ca^{2+} concentration with hypoxia that initiates smooth muscle contraction and that it does so by a mechanism not involving carbonic anhydrase inhibition [166]. Acetazolamide may also act to minimize HAPE by stimulating alveolar fluid clearance as recently shown in rats [167].

Maggiolini et al. [128] have recently reported that dexamethasone and tadalafil (a long-acting phosphodiesterase type 5 inhibitor) were as equally effective (reduction of recurrence rate to less than 10%) as nifedipine in HAPE-susceptible subjects. The effectiveness of tadalafil was expected given the prominent role of NO in modulating HPV, as shown with acute hypoxia or at high altitude with sildenafil [168], but the efficacy of dexamethasone was not so certain. Dexamethasone was chosen, on the basis of much animal work [23], as it might be a more selective agent in upregulating alveolar epithelial sodium and water reabsorption than salmeterol and so interpretation of its results would not be confounded by any potential ventilatory stimulation or HPV inhibition known for β_2 adrenergic agonists. The potent prophylactic effect of dexamethasone, however, was mediated by an equally striking reduction in PA pressures as in the tadalafil group, and even better arterial oxygenation. What appears to be a leading explanation for the efficacy of dexamethasone is its ability to upregulate pulmonary vascular eNOS and NO production, which was recently shown in isolated PA endothelial cells [169] and indirectly suggested by higher urinary cGMP excretion in patients treated with dexamethasone for HAPE prophylaxis [128]. Evidence in this same study for a sympatholytic effect of dexamethasone (lower heart rates) may have been another contributing factor to the reduced PA pressures. Another relevant effect of dexamethasone is increased surfactant production and secretion, which is used to enhance lung function in premature infants, but is also demonstrable in adult lungs [170]. Increased surfactant production would have possibly two salutary actions. By increasing the production of alveolar lining fluid surfactant, dexamethasone reduces surface tension, which in turn reduces negative forces at the air-liquid interface and thus lowers the alveolar-capillary transmural pressure difference [171]. This mechanism may explain the reduction in vascular permeability in hypoxic mice treated with dexamethasone in which no changes in PA pressure were reported [103]. Thus, dexamethasone may act in numerous ways to prevent HAPE; via its enhancement of NO production, decreased pulmonary vascular sympathetic tone, upregulation of alveolar sodium and water reabsorption mediated by corticosteroid-induced upregulation of alveolar epithelial apical membrane ENaC activity and basolateral membrane Na^+/K^+ ATPase activity [23], and enhanced surfactant secretion. All mechanisms

could lower PVR, either directly or by improving ventilation and raising alveolar and arterial PO₂.

5.4 Treatment

Immediate improvement of oxygenation is the treatment of choice. How to attain this depends on where HAPE occurs. In a remote area without medical care descent has the first priority. The tourist with HAPE in a skiing resort may stay at altitude if the arterial oxygen saturation can be kept above 90% with low-flow oxygen (2–4 L/min), monitoring by family or friends is guaranteed, and access to clinical care is close at hand. Relief of symptoms is achieved within hours and complete clinical recovery usually occurs within 2–3 days. Individuals with severe, advanced cases need to be evacuated to low altitude, where they may require prolonged hospitalization, especially if they have coexisting high-altitude cerebral edema.

Mortality is estimated to be around 50% when neither descent nor other treatment is possible. Without either oxygen or descent, portable hyperbaric chambers [172] or treatment with nifedipine (20 mg slow-release formulation every 6 h) should be initiated until descent can be accomplished. In a monitored clinical setting diuretics may be given, but this is not recommended in the field since the victims are often volume-depleted. In mountaineers with HAPE at 4,559 m persistent relief of symptoms, improvement of gas exchange, and radiographic appearance were documented over 34 h with 20 mg nifedipine every 6 h [29]. Nifedipine causes no significant side effects when administered either prophylactically or therapeutically in slow-release formulations. Inhaled NO, although presently technically difficult to provide, is effective [27], suggesting that other inhaled NO donors such as nitroglycerine, nitroprusside, and nitrite may be more practical. Whether inhalation of β₂-receptor agonists might be used in addition to nifedipine needs study, as does the use of any of the lesser studied prophylactic therapies, particularly the phosphodiesterase type 5 inhibitors.

6 Summary

HAPE is now well established as a consequence of HPV and sufficient transmission of high PA pressure and blood flow to portions of the pulmonary capillary bed, most likely due to regional unevenness in HPV with a possible contribution by venoconstriction. Although strong HPV is a characteristic shared by most individuals who develop HAPE, there probably can be no absolute resistance to HAPE, even in “non-susceptible” individuals, if the altitude and the ascent rate are

high enough or if other factors such as a concurrent respiratory infection transiently increase susceptibility. The fluid leak in humans with HAPE (and in animal models) affirms the concept proposed by West et al. 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. The study of HAPE has taught us much about 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 origins.

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