High-Altitude Pulmonary Edema (HAPE)

21

Robert B. Schoene and Erik R. Swenson

Abstract

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Introduction

Much of the clinical impact of acute altitude illnesses stems from fluid accumulation in interstitial spaces and nowhere is this more apparent than in the lungs as the edema escapes into the alveoli to cause life-threatening hypoxemia. This chapter will update our knowledge of HAPE over the past decade about the vasculature, alveolar epithelium, innervation, immune response, and genetics of the lung in hypoxia, as well as prophylactic and therapeutic strategies to reduce the toll of this most common alpine life-threatening illness.

Clinical Presentation

HAPE has an incidence of 0.2–15 % depending on altitude, ascent rate, exertion, gender, age, infection, individual susceptibility, and underlying health problems associated with pulmonary hypertension [1]. With past radiographically proven HAPE, the incidence may approach 60% [2]. Men are more susceptible than women [3], reflecting possibly the advantages of ventilatory stimulation from progesterone [4] and lesser hypoxic pulmonary vasoconstriction (HPV) from estrogen [5]. HAPE has no age dependence, although aging-related increases in pulmonary vascular resistance (PVR), which might also

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extend to HPV, would predict greater HAPE susceptibility. Although HAPE can develop in sedentary persons, exercise [6] and its pulmonary hemodynamic consequences (discussed below) are important precipitating factors.

Symptoms, signs, and physiologic changes in lung function typical of pulmonary edema [1–3, 7] evolve in 2–4 days after ascent, often preceded or accompanying AMS (see Chap. 20), but can occur later with further ascent. Arterial saturations can fall as low as 40 % and PaO_2s in the low 20 mmHg range. HAPE in its severest stage with profound hypoxemia can lead to high-altitude cerebral edema [8]. Repeat occurrences of HAPE do not always involve infiltrates in the same areas, which suggests that fixed structural aspects of lung parenchyma or vessels do not account for the timing of edema or its locale [9]. A special exception is unilateral absence of a pulmonary artery, in which edema always occurs in the contralateral lung receiving the entire cardiac output [10].

It has been suggested that many persons (50–75 %) may have subclinical HAPE that resolves spontaneously despite remaining at altitude [11–13]. This incidence equals that of AMS, which itself can cause mild gas exchange impairment [14] by unknown mechanisms perhaps related to altered autonomic influences on the pulmonary circulation and/or airways leading to ventilation-perfusion mismatching. Subclinical HAPE may be considerably overestimated without radiography [15] because indirect measures of interstitial edema such as spirometry, closing volume, and/or transthoracic impedance can vary for other reasons related to mountaineering including intense exercise and increased cardiac output, cold/dry air-induced bronchoconstriction, and hypocapnia [16]. With radiographically mild HAPE, only modest abnormalities were detectable [15] suggesting many lung function parameters are not sensitive enough to detect small changes in interstitial fluid and may require high-resolution tissue density measurements by CT or MR imaging. Reentry HAPE occurs when long-term high-altitude residents return to high altitude following a brief low-altitude sojourn. It has a strong familial basis and afflicts children more than adults [17], perhaps due to a twofold greater magnitude of HPV in preteen children (age 6–9) compared to teenagers (age 14–16) when tested 40 h after ascent to high altitude [18].

Pathophysiology

From its first modern descriptions, pulmonary hypertension and HAPE have been inextricably linked suggesting a primary hemodynamic basis. However, an inflammatory reaction and differences in hypoxia-sensitive, active alveolar fluid reabsorption may at times be contributory.

Hemodynamics

Mean PA pressures by catheterization in untreated HAPE range from 35 to 95 mmHg with normal PA wedge pressures. Noninvasive echocardiographic estimations of systolic PA pressure substantiate these data [2, 19] and show no evidence for left ventricular systolic or diastolic dysfunction [20, 21]. Excessive PA pressure precedes HAPE [2] and any interventions (descent, oxygen, or drugs) which lower PA pressure improve gas exchange and outcomes [19, 22, 23].

HAPE susceptibles have several hypoxic responses putting them at risk; the most important is strong HPV. Although their resting PA pressures are at the high end of normal at low altitude, exaggerated responses with normoxic exercise and sleep [24, 25] point to a constitutional hyperreactivity of the pulmonary circulation (Fig. 21.1). Their relatives have not been studied, but children and their fathers at 3,450 m show similar PA pressure increases [26], suggesting HPV is, in part, genetically determined as is the hypoxic ventilatory response (HVR) [27]. The prevalence of heightened pulmonary vascular responsiveness in the general population may be as high as 10 % [28] and may contribute to the out of proportion pulmonary hypertension that develops later in life in patients with sleep apnea, heart failure, and chronic lung disease.

PA catheterization studies at 4,559 m [29] found the exaggerated rise in PA pressure in HAPE susceptibles at 4,559 m led to an increased microvascular pressure above 20 mmHg in those

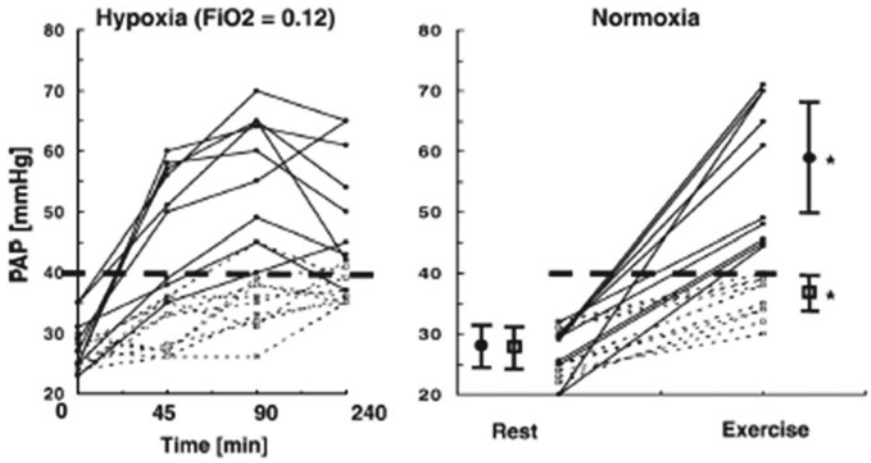

Fig. 21.1 PAP in HAPE-susceptible individuals (*continuous lines* and *filled symbols*) and in non-susceptible controls (*dashed lines* and *open symbols*) during exposure to normobaric hypoxia (*left*) and before and during exercise on a bicycle ergometer (*right*). The highest PAP recordings during exercise (75–150 W) are shown (From ref [62])

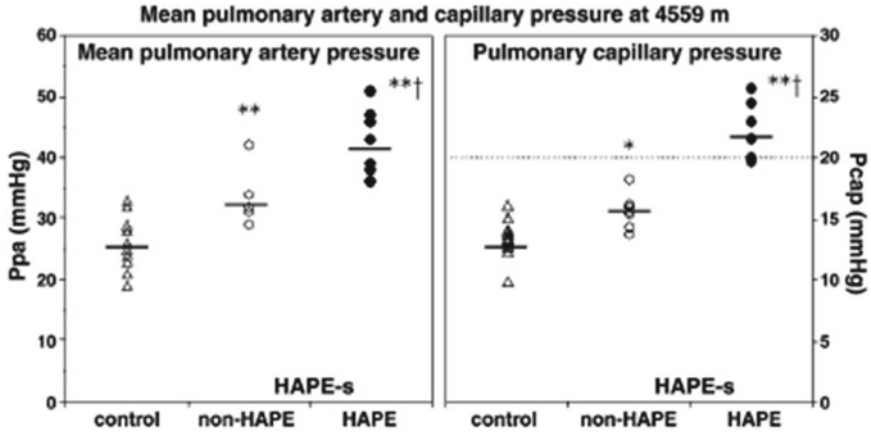

Fig. 21.2 Mean pulmonary artery pressure (P_{pa}) and pulmonary capillary pressure (P_{cap}) in 14 controls and in 16 high-altitude edema susceptible (HAPE-s) subjects at high altitude. HAPE-s is further divided in those who developed HAPE (HAPE) and those who did not develop HAPE (non-HAPE). *Bars* indicate the mean values in each group. $^{*}p<0.05$, $^{**}p<0.01$ vs. control, $^{\dagger}p<0.01$ vs. non-HAPE

developing HAPE (Fig. 21.2). This threshold for edema is similar to animal work in showing a PO_2-independent microvascular pressure of 17–24 mmHg [30]. It is interesting that this same pressure range in normoxic rats imposed by left atrial pressure elevation also reduces active alveolar epithelial sodium reabsorption [31]; which is discussed below in the "Alveolar Fluid Clearance" section. It should be emphasized that microvascular pressure rather than upstream PA pressure elevation is more crucial because strong HPV alone need not necessarily lead to HAPE, as shown in a study of adults with a history of perinatal hypoxia [32, 33].

High hypoxic PA pressures and PVR in HAPE-susceptibles is the sum of many influences including those intrinsic to vascular smooth muscle, but also to neuro-humoral responses, lung volume, and vascular endothelium.

Neuro-humoral Responses: HAPE susceptibles have a lower isocapnic HVR set largely by

the peripheral chemoreceptors [34, 35], which results in lower alveolar and arterial PO_2s at the same P_IO_2, and thus a stronger HPV stimulus. Similar, but only indirect measures of lesser ventilatory response to hypoxia (lower arterial saturation and higher end-tidal CO_2) have been shown in a group of high-altitude adolescents with susceptibility to HAPE (reentry HAPE) when compared to resistant controls [36]. These data from awake subjects have now been also shown to apply to sleep in HAPE-susceptible persons at high altitude [37, 38]. Lower HVR also leads to a smaller fall in P_ACO_2 and less hypocapnic inhibition of HPV [39]. HVR and HPV may be linked in two ways. Lower arterial PO_2 itself may increase PA pressure because isolated hypoxic perfusion of the bronchial artery (supplying the vasa vasorum of pulmonary arteries) increases PA pressure [40]. This finding may be relevant to subjects with a patent foramen ovale (PFO) who have greater arterial desaturation at altitude and an apparently higher incidence of HAPE [41], despite the potential benefit of a right to left intracardiac shunt in minimizing PA pressure elevation. The second is a direct modulation of HPV by the peripheral chemoreceptors via pulmonary innervation. In mechanically ventilated animals, vagotomy [42] and carotid body ablation [43] increase HPV. In humans, the magnitude of poikilocapnic HVR as measure of peripheral chemoreceptor oxygen sensitivity was found to be inversely correlated to the magnitude of HPV [44]. Acute moderate hypoxia in humans causes diuresis and natriuresis which are correlated to higher HVR [45]. HAPE susceptibles have lower HVR and may be disadvantaged by a limited diuretic response [46], in part by greater activation of the renin-angiotensin system [47] and sympathetic nervous system [48], but also less chemoreceptor-mediated natriuresis.

Increased Sympathetic Tone: Increased sympathetic tone with hypoxia, especially in the absence of strong opposing peripheral chemoreceptor input, may also contribute to stronger HPV, in an analogous fashion to those with low HVR who are more susceptible to cerebral-mediated hypoxic ventilatory depression [49]. HAPE susceptibles have increased skeletal muscle sympathetic tone during hypoxia at low and high altitude [47], although this study, similar to the HPV studies, suffers from lack of control on the strength of the hypoxic stimulus due to HVR differences. Stimulation by cerebral hypoxia of the lung sympathetic innervation augments HPV [50] via alpha receptors [51] and HPV is reduced with autonomic blockade in some [52] but not in all studies [46, 47, 53, 54]. Isolated perfusion of the dog brain with hypoxic-hypercapnic blood causes intense sympathetic activation, increased PA pressures, and pulmonary edema [55]. The impact of this study is diminished somewhat by the use of hypoxic-hypercapnic blood, because cerebral hypercapnic hypoxia is a potent stimulus for sympathetic activation, which would be less with the arterial alkalemia and hypoxemia typical at high altitude.

Lung Volume: HAPE susceptibles have 10–15 % lower lung volumes and 30 % lower functional residual capacity (FRC) [34, 35, 56, 57]. FRC is the lung volume at which normal breathing and perfusion occur and lung volume itself is a determinant of PVR [58]. HAPE susceptibles show greater arterial desaturation while supine that resolves with high tidal volumes [35] indicative of a lower FRC. Their lower diffusing capacity [57, 59] is consistent with a smaller capillary bed and less recruitability. Lacking lung biopsies and pre-HAPE lung function measurements, it is not possible to distinguish whether they have intrinsically different lung structure or that an episode of HAPE heals with a small loss in volume and capillary bed.

Vascular Endothelium: There are differences of the vasculature itself in HAPE susceptibility, although it has not been studied whether differences in PA vascular smooth muscle responsiveness to hypoxia exist. Nitric oxide (NO) and endothelin 1 (ET-1) are key endothelial-derived vasoactive mediators. Lung NO production in hypoxia is reduced in HAPE susceptibles as measured in exhaled gas (Fig. 21.3), alveolar lavage fluid, and blood [60–63]. Systemic vascular endothelial NO generation as a surrogate for the pulmonary circu-

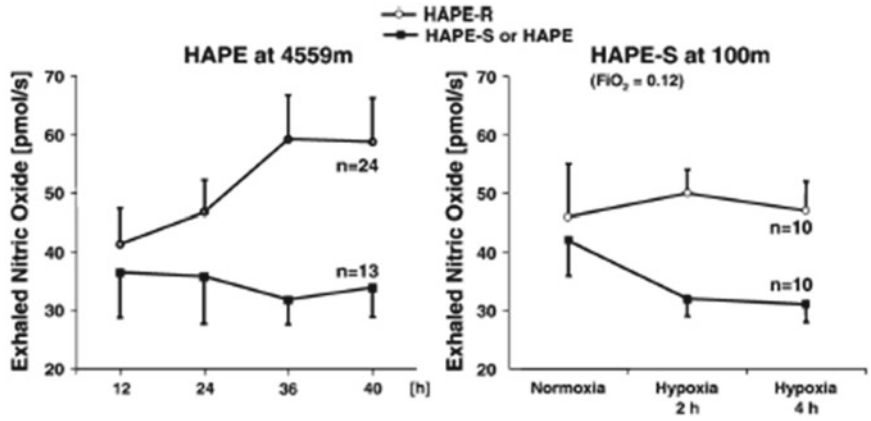

Fig. 21.3 (**a**) Exhaled NO after 40 h at 4,559 m in individuals developing HAPE (*left*) and in individuals not developing HAPE (HAPE-R) despite identical exposure to high altitude. (**b**) Exhaled NO in individuals with (HAPE-S) and without susceptibility (HAPE-R) to HAPE after 4 h of exposure to hypoxia ($FIO_2 = 0.12$) at low altitude (elevation 100 m) (From refs [61, 62])

lation is reduced more in hypoxic HAPE susceptibles [64, 65], possibly as a result of greater circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous metabolite of arginine and inhibitor of endothelial NO synthase [65]. Circulating ET-1 is elevated almost threefold at high altitude and to a greater degree in HAPE susceptibles and correlates with the rise in PA pressure [64–66]. Other vascular mediators studied in over 400 subjects at 3,500 m with likely hypertensive effect on the pulmonary vasculature are greater in HAPE susceptibles, including plasma concentration of serotonin, 8-iso prostaglandin F, renin, and aldosterone [65].

The study of HPV continues to identify new sensing, signalling and effector mechanisms and pathways, of which several warrant mention. In addition to the critical role of NO, two other endogenously produced gases, *carbon monoxide and hydrogen sulfide,* may be potentially important HPV modulators [67, 68], but have not been studied at high altitude or in HAPE susceptibles. Iron supplementation and iron chelation reduce and increase HPV respectively [69, 70], possibly via altered *HIF metabolism* [71]. In two rat strains with differing pulmonary hypoxic responses, HIF-1 activity and HIF-mediated protein expression were higher in the strain with lesser pulmonary hypertension [72]. In contrast, mice with heterozygous HIF 1-alpha deficiency have weaker acute and chronic hypoxic responses in isolated pulmonary vascular smooth myocytes and pulmonary vessels than wild type mice [73, 74]. Carotid body sensitivity to hypoxia in these same HIF 1-alpha deficient heterozygote mice is depressed [75], although this does not appear to diminish the HVR. Interestingly a recent report finds that low-altitude HAPE-susceptible individuals compared to HAPE-resistant persons and high-altitude natives in India have distinct polymorphisms in the EGLN-1 gene (HIF-prolyl hydroxylase-20) that acts to regulate HIF-1 alpha activity [76]. These polymorphisms are associated with differences in SaO_2 and pulmonary artery pressures at high altitude as would be predicted for HAPE susceptibility. Further supporting pharmacological evidence for HIF-1alpha mediation of HPV was demonstrated in mice by reduction in hypoxic pulmonary hypertension with digoxin, a known inhibitor of HIF-1alpha transcriptional activity [77]. At present it is not clear how HIF-dependent gene transcription affects HPV, but it likely involves alterations in pulmonary vascular smooth muscle calcium signalling [77].

A compelling case is emerging that hypoxia increases *reactive oxygen species* (*ROS*) generation (see Chap. 1), which is an upstream signal for HPV [78, 79]. While it is clear that altitude increases stable circulating markers of ROS production [80, 81] and may play a role in AMS, it also appears that persons with higher HPV

generate more ROS and less bioactive NO species across the lung [82]. In support of this, it was recently shown that HAPE-susceptible subjects have lower plasma concentrations of superoxide dismutase, an enzyme that converts oxygen radical (O_2^-) to H_2O_2, a less potent oxidant species [65]. Isolated human PA endothelial cells exposed to 3 % oxygen produce more hydrogen peroxide and become more permeable to albumin, both of which are diminished in vitro and in vivo by antioxidants [83].

Site(s) of Excessive Pressure and Leak in HAPE

Three theories have been proposed and none are mutually exclusive: (1) trans-arteriolar leakage, (2) hypoxic venoconstriction leading to capillary pressure elevation, and (3) uneven regional HPV with overperfusion in certain areas. Small arterioles are a site of leakage with markedly increased PA pressure [84, 85] possibly because their endothelial cells in vitro have a 20-fold greater permeability than more downstream microvascular arterial endothelial cells [86]. Pulmonary veins also constrict with hypoxia [87], thus increasing resistance and pressure downstream of the fluid filtration region. Uniform arteriolar and venoconstriction, alone or in combination, may contribute to edema formation; however, they cannot explain the patchy radiographic appearance of early HAPE unless there is regional HPV heterogeneity leading to uneven distribution of perfusion with high flow in those areas of lesser vasoconstriction. In these regions pressures might rise to the threshold of 17–24 mmHg [88], possibly aggravated further by increased venous resistance [89]. Recent investigations in non-exercising animals with microspheres [90] and humans with magnetic resonance imaging [91, 92] demonstrate that HPV is indeed uneven. Although exercise in hypoxia does not significantly further increase regional perfusion heterogeneity above that with hypoxia alone [93, 94], the much higher pressures [24, 25] should greatly increase the risk of injury in the more highly perfused areas (overperfusion edema).

The basis of uneven regional HPV is unknown but may involve inhomogeneous localization of smooth muscle, both in thickness and longitudinal distribution along the arterial tree. Intrinsic differences in local endothelial vasoactive mediator production or expression and heterogeneity of membrane ion channels and receptors may be also invoked, as exist for endothelial derived NO in the horse between dorsal and ventral lung regions [95]. It does not appear that uneven regional HPV in HAPE susceptibles is due to greater resting V_A/Q heterogeneity at low altitude, which would lead some regions having a lower P_AO_2 and to undergo a more precipitous drop with a fall in inspired PO_2 [56]. Unevenness of regional HPV may 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. There may be rapid remodeling and generalized homogenous muscular hypertrophy of all arterioles or greater NO production [61], both of which would lead to a more even blood flow distribution and microvascular protection. Another protective factor may be upregulated gene transcription and protein expression for collagen and other extracellular matrix constituents that strengthen the alveolar capillary barrier [96].

Although hypoxia even in the absence of pressure changes can also increase alveolar–capillary permeability [97, 98], the evidence best supports overperfusion edema occurring in some regions as a result of high blood flow under large driving gradients with resultant increased microvascular pressures exceeding the capacity of the lungs to maintain a fluid-free air space. What is lacking is definitive in vivo evidence that edema develops in areas of high flow. This will require studies using a single imaging modality capable of simultaneously resolving blood flow and changes in extravascular fluid content.

Inflammation

Alveolar lavage fluid in some mountaineers with HAPE [99, 100] revealing significant neutrophilia and elevations of several proinflammatory cytokines and neutrophil chemotactic factors engendered the idea that inflammation might be causal in HAPE. Work in hypoxic animals with viral [101] or endotoxin [102] administration showing

Table 21.1 Bronchoalveolar lavage 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 ($\times 10^3$/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 ($\times 10^3$/mL)	3	4	10	26*	623*
Total protein (mg/dL)	1.8	1.5	14*	34*	163*
PAP systolic(mmHg)	22	26	37*	61*	81*

Bronchoalveolar lavage (BAL) at 550 m and on the second day at 4,559 m in 8 control subjects (CONT) and in 9 HAPE-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 (pre-HAPE), 4 developed HAPE within 18 h after BAL. *$p<0.05$ vs. 550 m (From ref [62])

more edema and prevention of hypoxic edema with corticosteroid pretreatment, a classic anti-inflammatory therapy [103], further supported the concept. Ten percent oxygen given to rats causes leukocyte adhesion to systemic capillaries, ROS formation, depletion of endogenous NO, and increased permeability [104] and this can be blocked by dexamethasone [105]. The systemic capillary changes were due to local mast cell degranulation triggered by monocyte chemoattractant protein-1 generated by hypoxic alveolar macrophages [106]. Likewise, similar findings of increased ROS production, inflammation, and upregulation of the proinflammatory gene transcription factor, nuclear factor kappa beta (NFkB), were found in the lungs of rats and mice exposed altitudes >18,000 ft [83, 107–109] and were attenuated by antioxidant treatment [106]. More recently [110] it has been shown in mice exposed to 10 % hypoxia for 1 day that lung cells uniquely express hypoxia-induced mitogenic factor (MIHF), which is proangiogenic and vasoconstricting, but also stimulates release of the proinflammatory cytokine, monocyte chemotactic protein (MCP-1). However, the relevance of these studies to human HAPE is questioned because evidence for systemic capillary inflammation and leakage has not been found [111] and HAPE in humans develops at much lower altitudes and lesser hypoxia than studied in these rodent models.

The noninflammatory characteristics of alveolar fluid in some cases of HAPE [99] and no in vivo thrombin and fibrin formation except in very advanced HAPE [112] or differences in platelet activation with hypoxia between HAPE susceptibles and HAPE-resistant subjects [113] are more consistent with any inflammation occurring as a secondary response to alveolar–capillary barrier disruption and edema. When lavage was performed in climbers within a day of ascent to 4,559 m only mild alveolar hemorrhage and increased protein concentrations in the airspace (Table 21.1) (Fig. 21.4) were found both in those ill with HAPE (HAPE-ill) and in those who developed HAPE (pre-HAPE) within the next 24 h [62]. There was a strong correlation between the magnitude of pulmonary hypertension by echocardiography and hemorrhage and protein elevation in the alveolar space (Fig. 21.5). In contrast, there were no increases in alveolar neutrophils and proinflammatory mediators (tumor necrosis factor-α, interleukins 1 and 8) early in course of HAPE. Alveolar macrophages harvested 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 in vitro under normoxic or hypoxic conditions, before or after endotoxin stimulation [114], and in rat alveolar epithelial cells, macrophages, and pulmonary artery smooth muscle cells, mild hypoxia (5 % O_2) in fact led to an attenuation of proinflammatory gene and protein expression [115]. Lack of inflammation in early HAPE was recently shown in rats that were made to continuously walk slowly in hypobaric hypoxia (4,800 m) for up to 48 h. Despite greater hemorrhagic lung edema and histological evidence of capillary stress failure, there were no

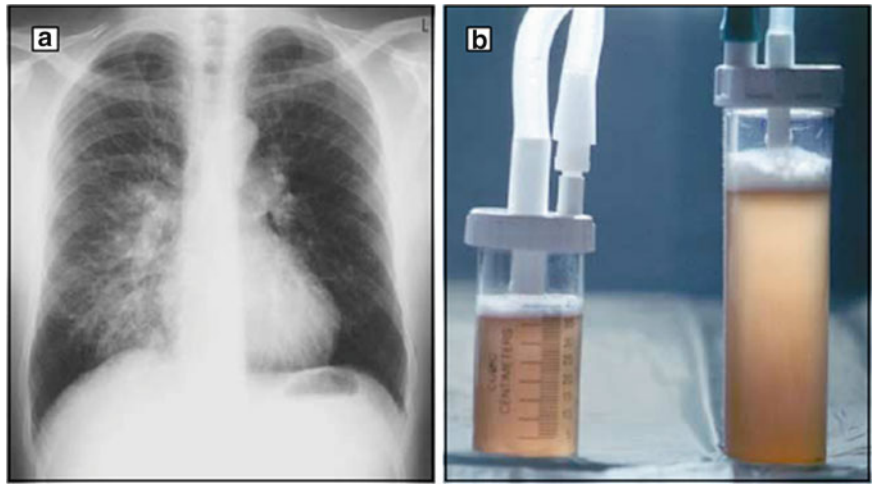

Fig. 21.4 Chest radiograph with bronchoalveolar lavage fluid aliquots (first and fifth) from a representative subject with early high-altitude pulmonary edema. The radiograph shows interstitial and alveolar infiltrates and the lavage performed after the X-ray was taken shows mild alveolar hemorrhage (From ref [62])

significant increases in leukotriene B4 and no correlations of edema or arterial hypoxemia with neutrophils in the lavage fluid [116]. In a model of greater hypoxic stress (10 % O_2) lasting 168 h but without exercise, inflammation as determined by increased lung mRNA for IL-1, IL-6, and TNF-alpha was not increased [117]. Increases in circulating interleukin-6 (IL-6) in humans at altitude [111, 118–120] continue to be taken as evidence for an inflammatory effect of hypoxia that might lead to HAPE [118]. This idea is problematic because exercising muscle releases IL-6 in proportion to intensity and duration of work both in normoxia and hypoxia [120, 121]. With passive ascent to high altitude, there is little to no increase in IL-6, even in HAPE-susceptible persons [122]. Although IL-6 is considered a classic proinflammatory cytokine, it may have equally important anti-inflammatory and endothelial permeability protective actions [121, 123]. Studies in IL-6 knockout and overexpressing mice should be instructive in determining the role of IL-6 at high altitude.

What initiates secondary inflammation is not clear? Sustained high pressures in untreated HAPE of sufficient duration may trigger inflammation [124] or the inflammation represents healing of a disrupted alveolar–capillary barrier that occurs in the most severe cases of HAPE. Alveolar hemorrhage, whose breakdown products including free hemoglobin and its subsequent degradation to heme metabolites are neutrophil chemoattractants [125]. These bind to danger and pathogen-associated molecular pattern cell surface proteins of the innate immune system to engage inflammatory signalling pathways [126].

Despite evidence, particularly in humans given above, against primary inflammatory alteration of the alveolar–capillary barrier in HAPE, animal models at much higher altitude or with greater normobaric hypoxia [105, 107, 108, 127] do support an element of initial co-contributing risk. Emerging evidence shows that severe hypoxia can induce inflammation via HIF-1 alpha and NFkB-linked gene regulation [127]. Thus, it may be possible that HAPE is primarily a pressure-related pathology, but if the hypoxia is severe enough, increased capillary permeability from activation of inflammatory cascades will also contribute to alveolar edema. Drugs such as nifedipine, the best studied pulmonary vasodilator for HAPE prevention (see below), could conceivably also act to limit inflammation and edema in the lung with severe hypoxia by suppressing NFkB, although in a rat study used to investigate this hypothesis the dosing was 50–100 times higher than that used in humans [128] and lower doses were not tested. Furthermore, it is likely

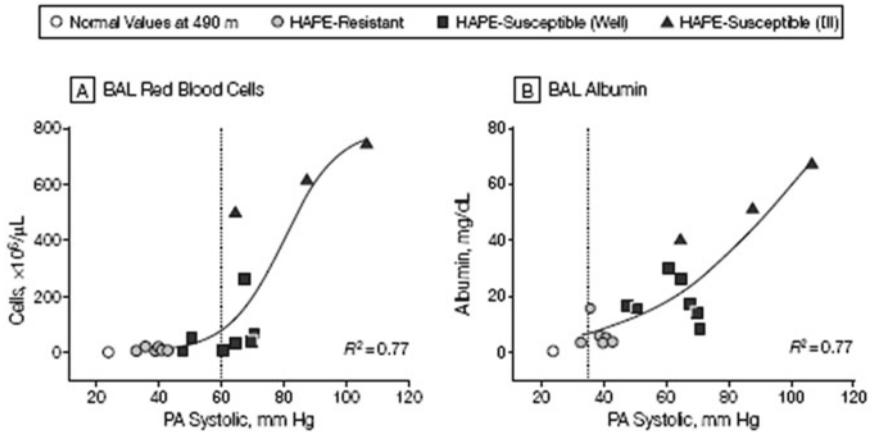

Fig. 21.5 Individual BAL red blood cell count and albumin concentrations plotted against pulmonary artery systolic pressures at high altitude (4,559 m). *BAL* indicates bronchoalveolar lavage; *HAPE* high-altitude pulmonary edema. The *vertical lines* denote a threshold systolic PA pressure (>60 mmHg) above which red blood cell (**a**) appear in the BAL fluid in contrast to the lower pressure (35 mmHg) at which albumin leakage occurs (**b**). The *open circles* in the *lower left* of both panels 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) (From ref [62])

that any concurrent process altering alveolar–capillary barrier permeability, such as preceding respiratory viral infections [129, 130], will lower the edema threshold and also explain why HAPE in humans can occur in some at a modestly low altitude [131].

Alveolar Fluid Clearance

Active sodium transport from alveolar space into the interstitium is important in normal lung fluid balance and a strong argument has been made for this process at high altitude. Hypoxia in vitro decreases transepithelial sodium transport by reducing expression and activity of the apical epithelial sodium channel (ENaC) and basolateral Na^+/K^+ ATPase [132] in cultured alveolar epithelial cells possibly by an impairment of beta-2 adrenergic receptor signalling [133, 134]. These and many other in vitro studies have used 1–3 % O_2 (reviewed in [135]), but recently it was found that 5 % O_2 had much less effect [115]. Whether or not this translates into reduced alveolar fluid clearance (AFC) with hypoxia in vivo is also conflicting. Some studies find depression of AFC [136, 137] acutely and mice partially deficient in ENaC develop greater accumulation of lung water in hypoxia [138]. However, in another study of rats exposed to 10 % O_2 for 5 days, there was no AFC depression in the first 3 days, after which it rose by 25–30 % [139]. Interestingly, a link between inflammation and HAPE may arise from viral infection-related downregulation of ENaC activity and diminished AFC [140]. In addition to hypoxia itself, raised intracapillary pressure around the level at which alveolar and interstitial fluid begin to accumulate also reduces active alveolar epithelial sodium reabsorption [31], but the mechanism is unknown.

Whether alveolar sodium transport differences underlie HAPE susceptibility has been addressed with transepithelial nasal potential (NP) differences as a surrogate for alveolar epithelial ion transport. Reduced NP differences indicative of decreased sodium reabsorption by ENaC have been reported in HAPE-susceptibles [141–143]. This has been questioned because NP differences between HAPE-susceptibles and controls at high altitude could not be attributed to differences in ENaC activity [143–145], but rather to differences in chloride secretion, which contributes a large fraction of the NP difference in the nasal mucosa, but not in the alveolar epithelium. The role of the cystic fibrosis transmembrane regulator (CFTR), a chloride channel and possible path-

way for chloride reabsorption accompanying reabsorbed sodium, has not been explored in HAPE susceptibility, but in rats beta-2 adrenergic receptor-mediated upregulation of CFTR function is necessary for increased alveolar fluid reabsorption [146] and newborn pigs with either heterozygous or homozygous CFTR gene knockout (but before the onset of lung pathology) have reduced alveolar sodium reabsorption [147]. Further evidence of the role of beta-2 adrenergic receptor-mediated lung fluid reabsorption was found in humans, in which circulating lymphocyte beta-2 adrenergic receptor density increase correlated with greater decrease in lung water during a 17-h normobaric hypoxic exposure [148].

To assess the relevance of active alveolar epithelial fluid reabsorption, inhaled salmeterol and oral dexamethasone, both of which are known to upregulate membrane ENaC and Na^+/K^+ ATPase (reviewed in [149, 150]), were studied at 4,559 m. Both drugs reduced HAPE in susceptible climbers [141, 151] when the drugs were begun one day before ascent. Owing to multiple actions of beta-2 adrenergic agonists (HPV inhibition, stimulation of HVR and ventilation, tightening of cell-to-cell contacts, and upregulation of NO production [152–155]), the contribution of enhanced active AFC to the positive outcome of the salmeterol study remains uncertain. Protection by dexamethasone [151] was not corroborated with indirect measures of enhanced active alveolar sodium and fluid reabsorption (NP difference and expression of leukocyte mRNA for sodium transporting proteins), but rather to a surprising reduction of PA pressure discussed below. It still remains the case that we need more selective and specific drugs to evaluate the role of active AFC in HAPE. In addition to deleterious effects of reduced NO in HAPE-susceptibles on PVR, NO may have a permissive and stimulatory effect on alveolar Na^+ reabsorption as shown in cell culture studies [156]. Two studies [157, 158] of endothelin add another face to this vasoconstrictor, that of inhibiting AFC by activation of endothelial cell ET-B receptors. The clinical importance of this possible effect of ET-1 on AFC and HAPE awaits human studies with selective ET-B receptor antagonists, because three studies at high altitude with bosentan (a nonselective ET-A/B receptor antagonist) have yielded conflicting results on PA pressure, exercise capacity, and gas exchange [66, 159, 160].

Unresolved questions surrounding the importance of active alveolar fluid reabsorption in HAPE are whether a reduced capacity is central in the earliest stages of the disease by failing to maintain sufficient airspace clearance or only later after the onset of edema. In the first case, then agents stimulating fluid reabsorption would be useful in prevention, but if the latter then these likely would alone be only effective treatment. Another is whether interstitial and alveolar edema, either alone or in combination with reduced alveolar PO_2 occurring with consequent lower local ventilation in these areas, link reduced fluid reabsorption to increased pulmonary vascular tone.

Mechanisms of Increased Alveolar–Capillary Barrier Permeability

Traditionally, pulmonary edema has been categorized as non-cardiogenic (increased permeability with exudative characteristics: high protein concentrations and inflammatory mediators with normal or only modestly elevated intravascular pressures) or cardiogenic (elevated hydrostatic pressures leading to a noninflammatory protein-poor transudative leak). Lavage and catheterization findings in nascent HAPE [29, 62] reveal characteristics of a hydrostatic but non-cardiogenic noninflammatory edema suggesting pressure-induced alterations to the normal permeability of the alveolar–capillary barrier or frank traumatic injury.

Stress Failure

Earlier work [161, 162] established that cardiogenic edema does lead to alveolar protein accumulation. The concept was further advanced for HAPE [163], when it was shown that discrete ultrastructural disruptions in the alveolar capillary barrier develop in rabbit lungs with very high transmural pressures typical of severe HAPE. These included disruptions in cell membranes,

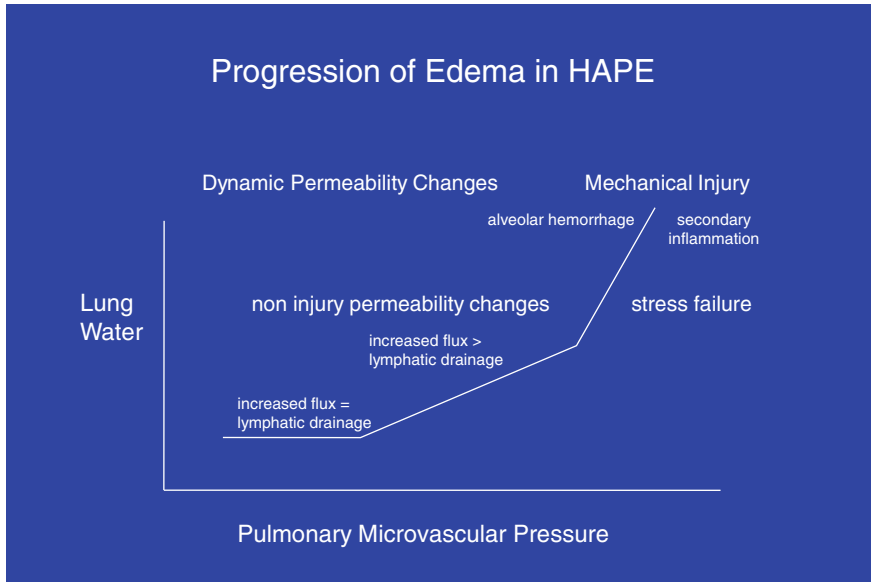

Fig. 21.6 Schematic sequence of events in the progression of edema with pulmonary artery pressure rise in HAPE from dynamic changes in alveolar capillary barrier permeability to mechanical injury

between cells, and in the basement membrane. These changes, also shown in rats exposed to rapid simulated hypobaric "ascents" to 8,800 m [164] for 1 day and to 4,700 m for 2 days with exercise as an additional stress [116], were termed capillary "stress failure" and ascribed to stretch and deformation of the extracellular collagen matrix in excess of their load-bearing capacity. Despite their traumatic-like appearance, even allowing red cell egress, these discontinuities can quickly close with pressure reduction [163]. It has been proposed that these 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 whose VEGF receptors are activated to promote vascular leak [165]. Elevated serum VEGF concentrations, however, have not been detected in patients with HAPE [166] or in HAPE susceptibles at high altitude [122].

Dynamic Alterations in Permeability

Before the onset of the obvious injurious changes in the alveolar capillary barrier noted above, there is an earlier phase of less severe hydrostatic pressure-induced permeability changes in the intact barrier (Fig. 21.6). This is evidenced by the fact that beta-adrenergic agonists [167] and gadolinium [168] reduce normoxic hydrostatic edema at constant vascular pressure. However, in a rat model of hypoxic edema at constant vascular pressure, terbutaline did not prevent the hypoxic permeability increase [97] suggesting hypoxia may limit beta-adrenergic signaling [133, 134]. Other factors such as hypoxic degradation of the glycocalyx lining the luminal surface of the vascular endothelium, which serves as a barrier to fluid extravasation [169, 170], may be involved. Vascular permeability changes with hypoxia are partially opposed by endothelial cell expression of adrenomedullin-2, a peptide that is upregulated by HIF-1 and is protective in other forms of lung injury [171], and by sphingosine-1-phosphate, an endogenous lipid that promote barrier enhancement via actin and junctional protein rearrangement [172]. Dynamic changes in transcellular leakage via vesicle formation and fusion to create pathways that traverse the cell [173, 174] and paracellular pathways via alterations in gap junction assembly [175] arise from signals initiated when cells are deformed by pressure or stretch. These responses may represent a preemptive attempt of the alveolar–capillary barrier to

lower stress forces temporarily and prevent damage to the basement membranes [176] and precede the more profound "stress failure" changes. There was no correlation between ultrastructural lesions and leakiness [177] suggesting that much of the permeability changes are not due to histologically evident stress failure disruptions. Lavage data at high altitude in climbers and in subjects before and after hypoxic exercise [62, 178] support this in showing a very mild protein leak even in the HAPE-resistant subjects (Table 21.1).

If hydrostatic forces persist, then gene upregulation and production of collagen and other extracellular matrix proteins are initiated to strengthen and remodel the alveolar–capillary barrier within hours [96]. These observations may explain the rapid recovery from HAPE and the protection from recurrence when reascending only several days later [179]. In reentry HAPE, there may be a reverse de-modeling of the vasculature when these people descend which then puts them at risk upon returning to high altitude.

Prevention and Treatment

Ascent Rates and Activity Level

Slow ascent is the most effective form of prevention even in susceptible individuals [1]. Persons should not ascend with any symptoms of altitude illness and should descend when mild symptoms do not improve after a day of rest. Vigorous exercise should be avoided during the first days by individuals with HAPE susceptibility and by those with symptoms of altitude illness or after a rapid ascent to altitudes above 3,500–4,000 m. Those with unilateral absence of a pulmonary artery [10], pneumonectomy [180], upper airway obstruction [181], cardiopulmonary conditions predisposing to pulmonary hypertension [1], or those with hypoventilation syndromes [182, 183] should be very circumspect about heavy exertion. As pointed out earlier, susceptibility to HAPE may be increased during and shortly after any infection.

Table 21.2 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 Na^+/H_2O reabsorptive capacity
Ventilatory and renal
• Lower hypoxic ventilatory responsiveness (HVR)
• Possibly reduced natriuretic response to acute hypoxia

Prediction of Susceptibility: Phenotypic and Genotypic Characteristics

Although as a group, HAPE susceptibles have physiological characteristics and responses to hypoxia that arguably set them at risk (Table 21.2), these responses are not easily tested except in specialized laboratories. Systolic pulmonary artery pressure in hypoxia (2 h at an F_IO_2 of 0.12) identified HAPE susceptibles with a specificity of 93 % and a sensitivity 77 % [184]. Lung volumes and HVR did not improve the identification. Recently it was proposed that a brief 8 min bout of hypoxic exercise ($F_IO_2 = 0.12$ at 30 % VO_2 max) could identify HAPE susceptibility by a greater than 19 mmHg rise in PA systolic pressure by echocardiography [185]. This study, however, should be considered preliminary and needs validation in a larger group, due to the small numbers of subjects studied, the difficulty in assessing PA pressures by echocardiography during exercise, and the fact that increases rather than absolute pressures were measured. Interestingly, systemic hypertension seems to be associated with stronger HPV [186], but this has not been explored as a risk factor in HAPE. Given the low prevalence of HAPE, such testing

described above may cause an overestimation of HAPE susceptibility. Further studies are needed to determine if a detectable PFO is a true risk factor for HAPE. In the last analysis, general screening of trekkers or mountaineers for HAPE susceptibility is not necessary, since illness can be avoided by slower ascent rates that permit adaptation of the pulmonary microvasculature to increasing pressures by remodeling [96].

There has been considerable interest in identifying genetic markers that might more readily predict HAPE susceptibility. Numerous candidates based upon reported and hypothesized differences in vasoactive and inflammatory pathways have been sought. The most studied thus far is vascular endothelial nitric oxide synthase (eNOS) and the data are far from compelling. Others include angiotensin converting enzyme (ACE), angiotensin receptor, surfactant proteins, coagulation factors, endothelin, tyrosine hydroxylase, HLA major histocompatibility loci, cytochrome P450, VEGF, bone morphogenic protein receptor-2, heat shock protein, beta-2 adrenergic receptor, aldosterone synthase, and EGLN-1 or HIF-prolyl hydroxylase 2 (for reviews see [187, 188]). Although statistically significant differences have been found, the differences are often not large and could not be confirmed in other ethnic groups. Furthermore, in some cases we do not know whether the detected allele has any functional impact on the biology of the transcribed protein. The major difficulties for these genome studies are that HAPE susceptibility will likely not be limited to a single gene, studies to date are considerably underpowered, ethnic differences may exist, and non-genomic determinants may be equally important, such epigenetic modification, microRNA control of gene expression, and post-translational protein modification.

Pharmacological Prophylaxis

Drug prophylaxis decisions should focus on any previous HAPE occurrence and a risk-benefit discussion. Nifedipine which inhibits HPV is the drug of choice for a history of unquestionable HAPE when slow ascent is not possible [2]. High-dose inhaled salmeterol [141] is an alternative choice, although the dose shown to be effective may cause tremor and tachycardia and is only 50 % as effective as nifedipine. Efficacy in general in stimulating fluid reabsorption to limit pulmonary edema remains unproven as demonstrated in the failure of inhaled high-dose albuterol to hasten AFC in ARDS [189].

Acetazolamide, long used for AMS prevention, blunts or abolishes HPV in animals and man [190, 191]. It was successful in an animal model of mild HAPE [192] and in children in Colorado with reentry HAPE (Peter Hackett, personal communication). Acetazolamide did not lower PA pressure in Himalayan trekkers and because no control subjects became ill, it could not be ascertained whether it might prevent HAPE [193]. The failure to lower PA pressures, similar to another study of subjects also at altitude for 10 days before testing [194], suggests that acetazolamide is not effective in already partially or fully acclimatized subjects. Acetazolamide prevents hypoxia-mediated increases in PA smooth muscle cytosolic calcium by a mechanism not involving carbonic anhydrase inhibition [195]. In vivo, acetazolamide may act by stimulating AFC [196] and by its classic stimulant action to increase ventilation and alveolar PO_2, thus reducing the main HPV stimulus. Recently it was reported that thiadiazoles, such as acetazolamide, are ROS scavenging [197]. This may be relevant not only to how acetazolamide reduces HPV but another action of acetazolamide in reducing HAPE if it is proven that increased ROS production is causal. A controlled trial in HAPE susceptibles needs to be undertaken.

Tadalafil (a long acting phosphodiesterase-5 inhibitor) was equally effective [151] in HAPE susceptibles as nifedipine in reducing the recurrence rate to <10 % vs. the 50 % effectiveness of salmeterol. The effectiveness of tadalafil was unsurprising given it blocks cGMP breakdown (the mechanism of action of PDE-5 inhibitors in amplifying NO effects to diminish HPV), as shown with sildenafil [198]. In addition to the vasodilatory effect of NO, increased NO or cGMP reduces pulmonary vascular endothelial permeability [199], a finding that helps to explain

why inhibition of NO synthesis in the isolated perfused lung increases edema even when the perfusion pressure was held constant [200]. Despite the effectiveness of tadalafil in reducing HAPE occurrence in a susceptible population, sildenafil, another PDE-5 inhibitor, did not significantly reduce PA systolic pressure at 5,200 in a group of climbers without known HAPE susceptibility [201].

In the same study examining tadalafil, dexamethasone (a glucocorticoid) was 100 % effective in preventing HAPE [151]. By its reduction of HPV and improvement in arterial oxygenation, it increased hypoxic exercise capacity [202]. Dexamethasone was chosen because it was thought that it might be more selective and specific in upregulating alveolar fluid reabsorption than salmeterol. Its potent prophylaxis, however, was mediated by a striking reduction in PA pressures as in the tadalafil group, but with even better arterial oxygenation both awake [151] and during sleep [37]. A leading explanation for its efficacy is its ability to upregulate pulmonary vascular eNOS and NO production [203] as indirectly suggested by higher urinary cGMP excretion [151] and thus reduce PA pressure [19] and strengthen the alveolar capillary barrier [199, 200]. A sympatholytic effect (lower heart rates) may be another contributing factor [151]. Another relevant effect is increased surfactant production and secretion even in adult lungs [204]. Surfactant reduces alveolar lining surface tension, which in turn reduces negative forces at the air–liquid interface and thus lowers the alveolar–capillary transmural pressure difference [205]. This mechanism may explain the reduction in vascular permeability in hypoxic mice treated with dexamethasone in which there was no change in PA pressure [103]. Dexamethasone-mediated effects may require gene transcription rather than more rapid non-genomic actions, because its efficacy was reduced [206] if given 1 day after arrival (late prophylaxis) rather than 1 day before as early prophylaxis.

Several other available drugs that inhibit or might inhibit HPV but have not been tested for efficacy in HAPE prevention include the other PDE-5 inhibitors, vardenafil and sildenafil; minoxidil, an activator of ATP-gated K^+ channels that reduces HPV in HAPE susceptibles [207]; statins [208], which upregulate endothelial cell NO production; ACE inhibitors [209, 210]; angiotensin II receptor blockers [211]; iron [70]; Rho kinase inhibitors [212]; and stimulators of cyclic GMP [213]. Although endothelin receptor blockers, such as bosentan, reduce HPV acutely [214], they are not advised presently due to their significant fluid-retaining activity [66, 159] as well as lack of efficacy with more chronic hypoxic exposure [159].

Lastly, biologic agents that reduce transendothelial permeability, such as keratinocyte growth factor-2 (KGF-2) via inhibition of apoptosis and upregulation of active salt and water transport as recently reported in a rat model of HAPE [215] may offer both prophylactic and therapeutic possibilities.

Non-pharmacologic strategies have received much less study, but two recent studies are worth noting. In the first study [216], staged ascent of subjects to a lower altitude for 7 days in a hypobaric chamber (Pb = 548 mmHg) before then ascending to 4,300 m (460 mmHg) resulted in a lower estimated mean PA pressure than that occurring without staging (25 vs. 37 mmHg). Ischemic preconditioning of one leg (arterial occlusion by cuff application for four cycles of 5 min occlusion followed by 5 min release), a technique that improves hypoxic and ischemic tolerance, reduced HPV by roughly 35 % 3 h later [217]. Whether either of these means of reducing HPV will be effective for HAPE prevention remains to be determined.

Treatment

The treatment of HAPE requires a proper diagnosis utilizing available history, physical exam, laboratory, and imaging data. Other possibilities including pulmonary embolism, bronchitis, pneumonia, congestive heart failure, and myocardial infarction should be entertained if symptom onset is too early or there are atypical features. Of these pulmonary embolism may be the most relevant alternate diagnosis. D-dimer appears to provide good discrimination because in a large

series at high altitude, only 1 out of 31 patients with HAPE had a diagnostic D-dimer elevation [218]. Recently for the diagnosis and monitoring of HAPE in the field, chest ultrasonography using a handheld portable unit was useful [219, 220] in detecting typical "comet tail" echogenic reflections arising from engorged septal lymphatics abutting the pleural surface indicative of pulmonary edema. The technique has promise but further validation in those with other underlying lung and cardiac diseases is needed.

The treatment of HAPE, unlike prophylaxis, includes a variety of strategies for which no controlled trials exist (reviewed in [221]). Immediate improvement of oxygenation is paramount. In a remote area without medical care, descent has first priority. The tourist with HAPE in an alpine resort may remain avoiding exercise if the arterial oxygen saturation can be kept above 90 % by low-flow oxygen (2–4 L/min) with monitoring by family or friends and easy access to clinical care if needed. A recent randomized controlled trial of nifedipine and oxygen vs. oxygen alone for soldiers with HAPE brought down to 1,370 m found no difference in outcomes [222]. Relief of symptoms is achieved within hours and complete clinical recovery usually occurs within 2–3 days. Severe and advanced cases need to be hospitalized or evacuated to low altitude.

Mortality is around 50 % when either descent or other treatment is not possible [223]. Without either oxygen or descent, portable hyperbaric chambers [224] or a continuous positive airway pressure "helmet" [225] can be initiated. Treatment with slow release nifedipine should be started until descent is underway [23]. Potent loop diuretics, such as furosemide, are not recommended in the field because victims maybe already volume depleted and any further ensuing volume contraction will cause greater renin-angiotensin system activation and increase PVR [226]. Inhaled nitric oxide, although technically difficult to provide, is effective [19] suggesting that other inhaled NO donors such as nitroglycerin, nitroprusside and nitrite, or inhaled prostacyclin analogues may be more practical. Whether multiple drugs should be administered has not been formally tested, but they are nonetheless often employed.

Summary and Directions for Future Research

HAPE is well established as a consequence of exaggerated hypoxic 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 altitude gained and ascent rate are high enough or if other factors such as a concurrent respiratory infection transiently arise. The fluid leak in humans with HAPE (and in animal models) affirms the concept 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.

Further developments in HAPE pathophysiology and clinical management will be greatly abetted by work on several fronts. The first is development of a large animal model that better mimics the entire time course, physical activity, and extent and injury characteristics that occur in humans. Presently models of HAPE in smaller animals such as the rat show only slight increases in lavage indices of permeability (e.g., 2–3 fold elevation in alveolar protein vs. the 20–50 fold increase in humans), less alveolar hemorrhage, greater systemic permeability, and in many cases lack any pulmonary vascular measurements to better assess the sequence of events that leads to a permeability leak. Even a recent pig model [227] of 48 h of 10 % oxygen (but without exercise) showed only modest increases in permeability and gas exchange abnormalities. Second, in order to assess definitively whether active alveolar sodium reabsorption plays a role in the development and resolution of HAPE, drugs and/or

genetic engineering in animals that only affect alveolar epithelial ion transport are sorely needed. Third, although many mediators of inflammation and HPV have been studied, their roles are judged largely on the basis of blood values, not changes in lung tissue or airspace concentrations, whose measurement may be more illuminating, especially in conjunction with known inhibitors or agonists. Fourth, given the astonishing results with dexamethasone in HAPE prophylaxis and PA pressure and exercise at high altitude, some of which may be attributed to blunting of the sympathetic nervous system response to hypoxia, the role of lung innervation in HAPE deserves more study. Lastly, many more persons with a history of HAPE are needed for genetic assessment of susceptibility. This may be advanced by the recent creation of a HAPE registry (http://iharc.partners.org) that hopefully will serve also as a database for genetic studies and analysis of preventative/treatment practices and as a source of subjects for controlled trials.

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