Chapter 25

HIGH-ALTITUDE PULMONARY EDEMA

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INTRODUCTION AND HISTORICAL BACKGROUND

High-altitude pulmonary edema (HAPE) is a noncardiogenic pulmonary edema that develops in susceptible people who ascend quickly from low to high altitude. The incidence of HAPE increases with the rate of ascent and the ultimate altitude attained. HAPE is a cause of significant morbidity in people who sojourn to high altitude, and although it is usually easily treatable, it remains the most common cause of illness-related death. (Please see Exhibit 19-1 in Chapter 19, Mountains and Military Medicine: An Overview, for definitions of sojourners, trekkers, climbers, and other categories of visitors to mountain environments.)

Undoubtedly, HAPE has occurred and existed for as long as people have sojourned into the mountains, although it was not recognized as a distinct clinical entity until the 1950s and 1960s. A description of what would now be regarded as acute mountain sickness (AMS) appeared in Chinese documents dating back to 37 to 32 BC,[1] but not until the year AD 403 did the first "case report" of probable HAPE appear in a written document. Hui Jiao, a Chinese archivist, noted that his traveling companion in the Lesser Snowy Mountains, Hui Jing,

> was in a serious condition, frothing at the mouth, losing his strength rapidly and fainting away now and then. Finally he dropped dead on the snowy ground.[2(p58)]

Altitude illness remained a relatively uncommon and obscure problem for several centuries; largely because people had little interest in venturing into the mountains and as means of rapid transportation were not yet available, the few who did were unable to travel high enough and quickly enough to become symptomatic. Mountaineering became more popular in the mid to late 19th century; consequently, the scientific and medical community became interested in investigating the physiological and pathophysiological effects of exposure to hypobaric hypoxia. In 1891, Dr Etienne Henri Jacottet ascended Mont Blanc (on the common border of France, Italy, and Switzerland) to make scientific measurements on the summit. He became quite ill but refused to descend so that he could "observe the acclimatization process" in himself.[3] He died soon thereafter; autopsy revealed "a suffocative catarrh accompanied by acute edema of the lungs."[3]

It was not uncommon for mountaineers to develop severe dyspnea at high altitude, particularly if they had ascended quickly and were engaged in strenuous activity; however, their symptoms were usually attributed to pneumonia or heart failure.[4,5] Railroads were built into the mountains—particularly in areas of mining such as the Andes of South America—early in the 20th century. For the first time, people could be transported rapidly from low altitude to high altitude. Dr Thomas Ravenhill, a physician working for a mining company in Chile, published the first comprehensive description of altitude illness in the English medical literature in 1913.[5] He depicted three types of *puna* (ie, altitude illness): normal, nervous, and cardiac. These descriptions are consistent with what would now be identified as AMS, high-altitude cerebral edema (HACE), and HAPE, respectively. Symptoms of cardiac puna included severe dyspnea, cough productive of white frothy or sometimes blood-stained sputum, cyanosis, and crepitations.[5,6] In a South American publication in 1937, Hurtado[7] described a case of pulmonary edema occurring in a resident of high altitude who visited sea level briefly and became ill shortly after returning to his native environment. Lizarraga[8] reported several similar cases of HAPE in 1955. Although Hurtado mentioned these cases and speculated on the mechanism of HAPE in the American journal *Military Medicine* in 1955,[9] not until Charles S. Houston, MD, published a case report in the *New England Journal of Medicine* in 1960[10] was HAPE brought to the attention of the English-speaking medical community at large.

The military relevance of HAPE is best illustrated by the experience of the Indian Army during the Sino–Indian border conflict in the 1960s, when the incidence of HAPE was noted to be as high as 15.5% in a group of "fresh inductees" who were rapidly transported to altitudes between 3,355 and 5,490 m (11,000–18,000 ft).[11,12] Morbidity and mortality from HAPE were significant, and a commanding general was one of several who died of the disease.[13] The threat posed by HAPE to military personnel who could be stationed at high altitude was well recognized by military physicians in the United States at that time.[14] Since the mid 1980s, Indian and Pakistani military forces have been engaged in a border conflict in northern Kashmir at altitudes between 5,185 and 5,490 m (17,000–18,000 ft); both sides have acknowledged that about 80% of casualties were caused by the harsh environmental conditions.[15] Mortality from HAPE has been reported to be as high as 44% when descent is not possible and supplemental oxygen is not available[16]—conditions that may be encountered in a combat situation.

The basic altitude physiology and the pathophysiology of altitude illness in general have been extensively reviewed in previous chapters of this textbook. The focus of this chapter is the clinical presentation, pathophysiology, and treatment of HAPE. Many other reviews in the medical literature present HAPE from different perspectives and provide some supplementary material.[4,6,13,17–25]

CLINICAL PRESENTATION

Incidence and Setting

The incidence of HAPE depends on the rate of ascent and the altitude achieved (Table 25-1).[12,13,17] The reported range of incidence is from an estimated 0.01% in people who traveled from low altitude to Vail, Colorado (2,501 m [8,200 ft]),[26] to 15.5% in a group of male Indian soldiers who were transported rapidly to between 3,355 and 5,490 m (11,000–18,000 ft).[11] Children of both genders appear to be more predisposed to HAPE than adults,[27] but the overall incidence of HAPE in adult women is much lower than in men.[26,28] Other factors that are believed to contribute to the development of HAPE include vigorous exertion and exposure to the cold,[11,13] although in one case series HAPE occurred more often in sedentary subjects than in those who had recently exerted themselves.[12] People who have experienced a previous episode of HAPE have a 60% to 70% likelihood of recurrence on reascent to high altitude.[29–31]

HAPE occurs in two common settings:

1. in residents of sea level or relatively low altitude who ascend to high altitude; and
2. in high-altitude natives (or people who reside at high altitude for at least several months) who descend to low altitude, stay for a period of time, and then reascend to high altitude.

These different manifestations of HAPE have been referred to as Type I and Type II but are more commonly called "HAPE" and "reentry HAPE," respectively. It has been suggested that these "variants" are epidemiologically different[26]; however, not enough data are available to substantiate this hypothesis. Singh and colleagues[11] stated that the incidence of HAPE was similar in "fresh inductees and reinductees"[11(p229)] to altitude. The relative incidence and prevalence of HAPE and reentry HAPE reported in the literature are probably more a re-

TABLE 25-1

INCIDENCE OF ALTITUDE ILLNESS IN VARIOUS EXPOSED GROUPS

Study Group*	Number at Risk per Year	Sleeping Altitude (m)	Average Days to Reach Sleeping Altitude From Low Altitude	Maximum Altitude Reached (m)	Percentage with AMS	Percentage with HAPE and/or HACE
Visitors to western US states	30 million	~ 2,000 ~ 2,500 ≥ 3,000	1–2	3,500	18–20, 22 27–42	0.01
Mt Everest trekkers	6,000	3,000–5,200	1–2 (fly in) 10–13 (walk in)	5,500	47 23	1.6 0.05
Mt McKinley climbers	800	3,000–5,300	3–7	6,194	30	2–3
Mt Rainier climbers	6,000	3,000	1–2	4,392	67	‡
Indian army soldiers	Unknown	3,000–5,500	1–2	5,500	†	2.3–15.5

AMS: acute mountain sickness; HACE: high-altitude cerebral edema; HAPE: high-altitude pulmonary edema
*See Exhibit 19-1 in Chapter 19, Mountains and Military Medicine: An Overview, for definitions of groups
†Reliable estimate unavailable
‡No data available
Adapted with permission from Hackett PH, Roach RC. High-altitude medicine. In: Auerbach PS, ed. *Wilderness Medicine*. 4th ed. Philadelphia, Pa: Mosby; 2001: 3.

flection of the demographics and geographical location of the population being studied than a representation of two distinct clinical entities, however.

Most early reports from South America concentrated on native highlanders and, as such, most of their cases were of the reentry HAPE variety.[7,8,31,32] In these cases, the average length of stay at a lower elevation prior to returning to high altitude was about 12 days, although one individual had remained at low altitude for 5 months. HAPE has also been reported to occur after descents as brief as 24 hours. Reentry HAPE usually developed between 3 and 48 hours after arriving at altitudes between 3,660 and 4,575 m (12,000–15,000 ft). Most episodes occurred within the first 24 to 36 hours of reexposure to altitude but can occur several weeks after ascent, particularly at extreme altitude. This time course and altitude profile is also similar for lowlanders who ascend rapidly to high altitude. Although the incidence of HAPE is low below altitudes of 3,050 m (10,000 ft), Maldonado[33] described a number of people who developed Type II HAPE in Bogotá, Colombia, at an altitude of 2,641 m (8,660 ft), illustrating that the diagnosis of HAPE should be considered in the appropriate clinical setting, even at relatively low altitudes. HAPE also occurs occasionally in people who have resided at high altitude for several months and have not recently changed elevation, although this is unusual.[11,12]

Symptoms and Physical Findings

The symptoms and findings of the physical examination in HAPE are similar to those seen in cardiogenic forms of pulmonary edema, although the illness may begin insidiously.[11,13,18] Early manifestations of HAPE include decreased exercise tolerance at altitude and a longer recovery period after exertion. Most victims of HAPE initially experience symptoms consistent with AMS, such as headache, lethargy and fatigue, nausea, and difficulty sleeping.[11,12,34] Then respiratory symptoms such as dyspnea on exertion, chest discomfort, and dry cough develop and begin to predominate the clinical picture. As the disease progresses, dyspnea is noticeable at rest and in severe cases, the cough becomes productive of blood-tinged, frothy sputum. Symptoms often develop and worsen during the night,[35] presumably because of decreased ventilation (and subsequent decrease in arterial oxygen saturation [Sa_{O_2}]), and redistribution of blood flow that occurs when subjects are in a recumbent position.[13] Signs and symptoms of HACE (discussed in Chapter 24, Acute Mountain Sickness and High-Altitude Cerebral Edema) may accompany HAPE, especially at higher altitudes.

Physical examination typically reveals tachypnea and tachycardia, with orthopnea and cyanosis becoming manifest in more severe cases.[12,31,32] A low-grade fever is often present.[12,27] Examination of the lungs reveals rales, often asymmetrical in distribution and initially located in the right midlung field,[13,17,18] but as the disease progresses, the rales spread throughout both lung fields. Of note, there is no accompanying evidence of cardiac failure such as a third heart sound or distention of the neck veins,[31] although the second component of the pulmonic heart sound is often palpable and accentuated.[12] Marticorena and Hultgren[36] developed a scoring system to grade the severity of HAPE based on clinical symptoms, signs, and radiographic findings (Exhibit 25-1). From a clinical and a research standpoint, their scoring system is useful in grading the severity of HAPE.

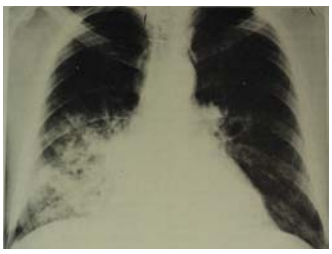
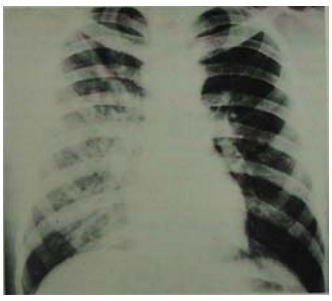
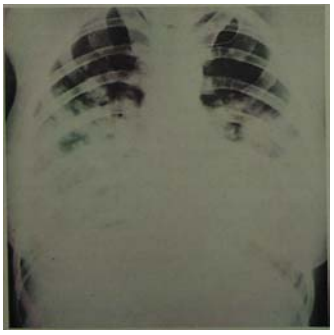
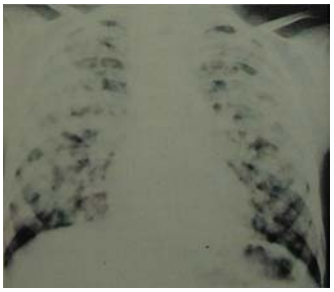
In 1971, Lenfant speculated that "a diffuse, asymptomatic pulmonary edema"[37(p1303)] was at least partially responsible for the ventilation–perfusion mismatching and gas-exchange abnormality often seen in people who ascend to high altitude. In support of this theory, Jaeger and colleagues[38] demonstrated that in a group of 25 male soldiers, thoracic intravascular fluid volume increased abruptly following rapid ascent to 14,000 ft, although none of these men had findings on physical or radiographic examination suggestive of pulmonary edema. The incidence of rales in trekkers in the Himalayas in another study was noted to be 23% overall; 40% of people with rales had no clinical evidence of AMS or HAPE.[39] These findings suggest that subclinical pulmonary edema occurs frequently in people ascending to high altitude. The true prevalence of subclinical HAPE, and the percentage of people with mild interstitial edema who eventually develop disease severe enough to be recognized clinically, is unknown.

Radiographic Findings

The chest roentgenogram findings in HAPE have been well described.[11,12,30,31,33,34,40,41] Although one study suggests that "[a] peripheral, often patchy or nonhomogeneous distribution of densities is typical,"[30(p665)] others emphasize the wide variety of findings that are seen in patients with HAPE. Infiltrates may be patchy or diffuse, unilateral or bilateral, and distributed primarily in a central or a peripheral location.[31,33,41] This diversity of radiographic abnormalities is most likely related to the stage of disease at which the roentgenogram was taken. It has been hypothesized that the infiltrates start patchy and peripheral, and as the disease

EXHIBIT 25-1

SEVERITY CLASSIFICATION OF HIGH-ALTITUDE PULMONARY EDEMA

Grade	Clinical Symptoms and Signs	Roentgenographic Findings and Example Chest Films
1. Mild	Minor symptoms with dyspnea on moderate exertion. May be able to perform light activity. Heartbeats per minute: < 110 Breaths per minute: < 20	Minor opacities involving < 1/4 of one lung field: 
2. Moderate	Symptoms of dyspnea, weakness, fatigue on slight effort. Cannot perform light activity. Headache with cough, dyspnea at rest. Heartbeats per minute: 110–120 Breaths per minute: 20–30	Opacities involving at least 1/2 of one lung field: 
3. Serious	Severe dyspnea, headache, weakness, nausea at rest. Loose, recurrent, productive cough. Wheezy, difficult respirations; obvious cyanosis. Heartbeats per minute: 121-140 Breaths per minute: 31–40	Opacities involving at least 1/2 of each lung field, or unilateral exudate involving all of one lung field: 
4. Severe	Clouded consciousness, stupor, or coma. Unable to stand or walk. Severe cyanosis. Bubbling rales present with copious sputum, usually bloody. Severe respiratory distress. Heartbeats per minute: > 140 Breaths per minute: > 40	Bilateral opacaties involving > 1/2 of each lung field: 

Adapted with permission from Marticorena E, Hulgren HN. Evaluation of therapeutic methods in high altitide pulmonary edema. *Am J Cardiol.* 1979; 43:308, 309.

progresses they become more diffuse, homogenous, and consolidated.[41] When the infiltrates are unilateral, they are more frequently located on the right side.[31,41] The symmetrical "bat-wing" distribution of edema, typically seen in cardiogenic pulmonary edema, is distinctly unusual.[34] Enlargement of the right ventricle has also been reported,[34,40] although other reports describe the heart size as being normal[30,33,42] or normal to minimally elevated.[41] Kerley B lines and pleural effusions are very unusual but may be observed in a minority of patients; when present, effusions usually develop in the recovery period.[41] Peribronchial and perivascular cuffing is almost always present.[41]

Main pulmonary arteries may be prominent and dilated in HAPE.[11,30,31,33,34,40,42] One Japanese study[40] compared the chest radiographs of 16 patients with HAPE, obtained at hospital admission, with those obtained following their recovery and documented a decrease in both the area and the volume of the main pulmonary artery, as calculated from the posteroanterior projection. Vock and colleagues[30] studied 25 male volunteers whose chest radiographs were taken at an altitude of 550 m (1,805 ft) and again at 6, 18, and 42 hours after they were rapidly transported to 4,559 m (14,958 ft). Eight of these subjects subsequently developed HAPE (six had experienced HAPE previously). Within 6 hours after arrival at high altitude, the diameter of the central pulmonary arteries increased by 17% to 30% in all subjects; there was no statistically significant difference in this measurement between the group that developed HAPE and the group that did not.[30] This observation suggests that dilation of the pulmonary arteries is characteristic in individuals acutely exposed to high altitude, and it should not be considered a finding that is unique to HAPE. In addition, this study documented the time course of radiographic evidence of HAPE, and the relationship between the extent of radiographic abnormalities and the presence of rales.

Changes consistent with the diagnosis of HAPE were generally present within 18 hours after arrival, and in all subjects except one, the infiltrates had progressed during the next 24 hours. Rales were absent in half the observations of subjects who simultaneously had radiographic evidence of HAPE, implying that the diagnosis of HAPE should not be excluded on the basis of normal lung sounds with auscultation. Conversely, rales were detected in several subjects with normal chest roentgenograms who later developed radiographic evidence of HAPE, indicating that radiographic changes may be insensitive in detecting early pulmonary edema and may lag behind the physical findings. Radiographic abnormalities may be expected to resolve very quickly (ie, within 24–72 h) with appropriate therapy.[11,13,27,32,42]

Ancillary Findings

Laboratory Findings

Several analyses of patients with HAPE that have reported blood test results have demonstrated that hematocrit and hemoglobin levels are normal.[12,26,27,33,34] One of these studies[34] noted that the hematocrit was lower on recovery, suggesting that hemoconcentration occurred during the acute illness, although another investigation[12] showed no change with recovery. Leukocyte counts are usually elevated[12,26,27,31,33,34] and frequently associated with a leftward shift of the granulocyte series.[12,26,33,34] Serum chemistries[33,34] and sedimentation rates[12,31,33] are typically normal; however, one study[34] reported a significant elevation of creatine kinase (CK), presumably secondary to muscle damage. Of five patients on whom CK isoenzyme analysis was performed, two had elevations of the CK-BB component (to about 1% of the total), which the authors of the study believed to be indicative of brain damage. Decreased serum iron levels, mild thrombocytopenia, and a slight increase in prothrombin time have also been reported.[34] Urinalysis results are not consistent, with some investigations reporting normal results[12,33] and others reporting increased specific gravity[31] and a preponderance of albuminuria.[34]

At a given altitude, Sa_{O_2} is significantly lower in people with HAPE, compared with those without.[30,43] At 2,745 to 3,355 m (9,000–11,000 ft), the mean Sa_{O_2} in HAPE subjects was 73.7%, compared with 90.6% in healthy controls[43]; and in another study conducted at 4,559 m (14,958 ft), these values were 59% and 80%, respectively.[30] Arterial blood gases (ABGs) typically reveal severe hypoxemia and respiratory alkalosis.[34,40,44,45] Kobayashi and colleagues[34] evaluated 27 patients who developed HAPE at altitudes ranging from 2,680 to 3,190 m (8,793–10.466 ft); mean ABG values within 3 hours of arrival at the hospital (altitude 610 m [2,001 ft]) were pH, 7.47; Pa_{CO_2}, 30.6; and Pa_{O_2}, 46.1.

Electrocardiographic, Hemodynamic, and Echocardiographic Findings

The electrocardiographic (ECG) tracings in patients with HAPE invariably reveal sinus tachycardia.[12,32,33] Findings suggestive of right ventricular strain and hypertrophy, such as right axis deviation, right

bundle-branch block, an S_1Q_3 pattern, and tall R waves over the right precordial leads have also been described.[31–33] A variety of changes in T wave morphology, to include diffuse flattening and inversion[12,33] as well as an increase in the size of the T waves in both the precordial and the limb leads,[32] have also been reported. Peaked P waves in leads 2 and V_1 or V_2 (suggestive of right atrial enlargement—thought to be caused by an acute increase in pulmonary artery pressure [PAP]) have also been noted.[31,32,42] Some studies have stated that except for sinus tachycardia, the ECG is usually normal,[12] whereas others noted that at least some of the abnormalities described above are present more often than not.[11,31–33] Q waves[12] or T wave changes in the standard (bipolar) lead I, the augmented limb lead aVL, and the precordial leads[31] are not characteristic of HAPE. On recovery, most patients' ECG abnormalities resolve,[31,33] although despite clinical improvement, T wave changes often persist for several weeks if the individual remains at altitude.[11,12,33] It should be noted that right axis deviation, T wave abnormalities, and P wave abnormalities have also been described in individuals without HAPE who were exposed to hypobaric hypoxia,[46,47] suggesting that these changes may be more closely associated with the degree of elevation of PAP than with the development of HAPE per se.

In 1962, Fred and colleagues[48] published the first report of hemodynamic data in a patient with HAPE. Cardiac catheterization in this patient revealed a markedly elevated PAP (68/39), which decreased substantially while the patient breathed 100% oxygen, and normal left atrial and pulmonary venous pressures. On the basis of these findings, they concluded that left ventricular failure was not the cause of edema formation, and also that the increased resistance to blood flow was largely due to hypoxic pulmonary vasoconstriction (HPV). Hultgren and colleagues[49] in 1964 and Roy and colleagues[44] in 1969 confirmed these findings and also demonstrated that the pulmonary capillary wedge pressure in HAPE was normal or low in all patients, thus providing further evidence that HAPE is not caused by cardiac failure or pulmonary venous constriction. Other, more-recent studies that have compared hemodynamic data during the acute illness and the recovery phase reveal that the resolution of infiltrates on the chest radiograph,[34,40] as well as improvement in Sao_2,[34] are associated temporally with the normalization of PAP.

Obtaining invasive hemodynamic measurements at high altitude is obviously problematic. Echocardiography has been employed in several studies evaluating pulmonary hemodynamic responses to hypoxia in subjects who have previously experienced HAPE (and are therefore HAPE-susceptible, discussed below in this chapter).[50–52] Echocardiography has also been utilized since the early 1990s in evaluating the effects on pulmonary hemodynamics and cardiac function of various pharmacological agents proposed for use in the prophylaxis and treatment of HAPE.[29,53,54] These studies demonstrated a marked increase in PAP in HAPE subjects and HAPE-susceptible subjects, compared with controls.

Bronchoalveolar Lavage Findings

In two separate studies, Schoene and colleagues[55,56] performed bronchoscopy with bronchoalveolar lavage (BAL) in 14 people (6 with HAPE, 4 with AMS,

TABLE 25-2

CONSTITUENTS OF BRONCHOALVEOLAR LAVAGE PERFORMED AT HIGH ALTITUDE

Substance Recovered	Controls (n=4)	Patients	
		AMS (n=4)	HAPE (n=8)
Total WBC (• 10^5/mL)	0.7 ± 0.6	0.9 ± 0.4	3.5 ± 2.0
Polymorphonuclear Leukocytes (%)	2.8 ± 1.5	2.4 ± 1.7	25.4 ± 20.0
Alveolar Macrophages (%)	93.8 ± 5.2	93.8 ± 3.4	67.4 ± 28.1
Total Protein (mg/dL)	12.0 ± 3.4	10.4 ± 8.3	616 ± 329.1

AMS: acute mountain sickness; HAPE: high-altitude pulmonary edema; WBC: white blood cells
Reproduced with permission from Schoene RB. High altitude pulmonary edema: Pathophysiology and clinical review. *Ann Emerg Med*. 1987;16:988.

and 4 without altitude illness) on Mount McKinley in Alaska, at an altitude of 4,400 m (14,436 ft). The results of these procedures are summarized in Table 25-2. Analysis of the BAL fluid revealed a 60-fold increase in high molecular weight proteins in HAPE subjects, compared with AMS subjects and controls, a finding consistent with increased permeability of the pulmonary vascular endothelium. Other notable findings included detectable levels of several potent chemical mediators in the HAPE fluid, including $C5_a$, leukotriene B_4 (LTB_4), and thromboxane B_2, as well as a substantial increase in total leukocytes (particularly neutrophils and alveolar macrophages). For the sake of comparison, subjects with severe HAPE have much higher protein concentrations and similar numbers of total leukocytes, albeit much lower numbers of neutrophils, than patients with another form of high-permeability pulmonary edema, adult respiratory distress syndrome (ARDS).[57] The implication is that although acute inflammation may not be as important in the pathogenesis of HAPE as it is in ARDS, it probably plays a role, possibly in the perpetuation of the permeability leak.

Several other studies[58–60] have confirmed the findings of protein, inflammatory cells, and various chemical markers of inflammation in BAL fluid of patients with HAPE.

Autopsy Findings

Autopsy results on several victims of HAPE have been published[11,32,34,42,61,62] and have consistently demonstrated (*a*) severe pulmonary edema, with bloody, frothy fluid present in the airways; (*b*) right atrial and ventricular distention and hypertrophy; (*c*) no left-sided cardiac enlargement; and (*d*) patent coronary arteries. In addition to being blood-tinged, the fluid found in the alveoli has been described as "proteinaceous,"[11] or protein-rich.[34] Other common findings include marked congestion and distention of the pulmonary vessels, with evidence of thrombi formation in small pulmonary arteries and septal capillaries. Although it has been speculated that the formation of thrombi may be involved in the pathophysiology of HAPE, research published in the late 1980s by Bärtsch and colleagues[63,64] suggests that in vivo fibrin generation is more likely an epiphenomenon of, rather than the cause of, edema formation.

Hyaline membranes are often[32,61] but not always[42] a characteristic of HAPE. As an aside, electron microscopy performed on the lungs of rats exposed to high altitude (barometric pressure [P_B] 265 mm Hg) for only 12 hours revealed the formation of multiple endothelial vesicles that contained a granular material.[65] Heath, Moosavi, and Smith[65] speculated that these "oedema vesicles" could conceivably exert a significant hemodynamic effect by protruding into the pulmonary venous capillaries; however, as no electron microscopy data have been published in humans, the significance of this finding is uncertain. In summary, the pathological findings described in HAPE collectively support the concept that rather than being cardiogenic in origin, the edema is of the "high-permeability" type, similar to the hemodynamic data and BAL studies mentioned above.

PATHOPHYSIOLOGY

Role of Pulmonary Hypertension

Although the exact mechanism of illness is unknown, most investigators believe that HAPE and the other major altitude illnesses, AMS and HACE, are caused by the *consequences* of exposure to acute hypoxia, rather than by hypoxia per se (Figure 25-1).[19,66–69] Perhaps the most important physiological effect of low ambient and arterial oxygen tensions relative to the development of HAPE is pulmonary vasoconstriction. Houston speculated in 1960 that HAPE was caused by elevated PAP secondary to anoxia, leading to failure of the left ventricle.[10] Although subsequent investigations of hemodynamics in patients with HAPE proved him wrong with regard to overt left ventricular failure (there is some reported evidence for ventricular dysfunction during exercise[70,71] and diastolic dysfunction at rest[72]), several lines of evidence suggest that pulmonary hypertension is critical to the development of HAPE.

Altitude Exposure and Pulmonary Arterial Pressure

The hypoxic pulmonary vasoconstriction response (HPVR), which is manifested by an increase in PAP, was initially described in an animal model (cats) in 1946.[73] One year later, Motley and colleagues[74] demonstrated that mean PAP increased from 13 to 23 mm Hg in five normal human volunteers following their exposure to a fraction of inspired oxygen (F_{IO_2}) of 0.1. Rotta and colleagues[75] first described the relationship between PAP and altitude in 1956. Not surprisingly, PAP rises as altitude increases (Figure 25-2) because of the associ-

ated decrease in inspired oxygen tension at higher altitudes. It should be emphasized, however, that the degree of this response is highly variable between individuals.[76–78] Those with exaggerated responses to hypoxia appear to be predisposed to developing HAPE.

People who have previously experienced HAPE have been the subject of many investigations, in an attempt to determine whether something unique or remarkable about their physiological response to hypoxia makes them susceptible to the condition. Hultgren, Grover, and Hartley[45] measured PAP in five HAPE-susceptible (HAPE-S) subjects at sea level and also 24 hours following their ascent to 3,100 m (10,171 ft), and demonstrated that their HPVRs were markedly exaggerated both at rest and during exercise, compared with what would be expected in normal individuals at that altitude. None of the subjects developed clinically apparent pulmonary edema, suggesting that elevation of PAP can occur prior to, rather than as a consequence of, the development of edema—a phenomenon that since then has been explicitly demonstrated.[29,53,78] Viswanathan and colleagues[79] evaluated the effect of breathing a hypoxic gas mixture ($F_{IO_2} = 10\%$) for 5 minutes in 51 HAPE-S subjects and 44 controls and also found greater HPVRs in the HAPE-S group. Although this finding was questioned by Naeije, Melot, and Lejeune[80] in 1986, more-recent studies[50–52,70,71,81] have repeatedly shown that HAPE-S individuals have a "constitutional abnormality in the pulmonary vascular response to hypoxia,"[51(p801)] which is even more pronounced during exercise.[50,70,71]

As yet, the constitutional abnormality responsible for the increased HPVRs in HAPE-S individuals has not been precisely defined, although research findings have identified several possible contributing mechanisms. One possible mechanism is an increased hypoxia-related sympathetic nervous system stimulation. Thus, Duplain and colleagues[78] found an increased rate of sympathetic nerve discharge that correlated with increased PAP in HAPE-S subjects, compared with control subjects at high altitude. Further, the increase in sympathetic nerve activity and pulmonary pressure preceded the development of HAPE in HAPE-S subjects. Another possible mechanism involves an imbalance in pulmonary endothelial vasoconstrictor and vasodilator mediators. Sartori and colleagues[82] demonstrated an increase of the pulmonary vasoconstrictor endothelin-1 at high altitude in HAPE-S subjects relative to normal control subjects, and the levels correlated with PAP. HAPE-S subjects have been shown to have decreased pulmonary production of

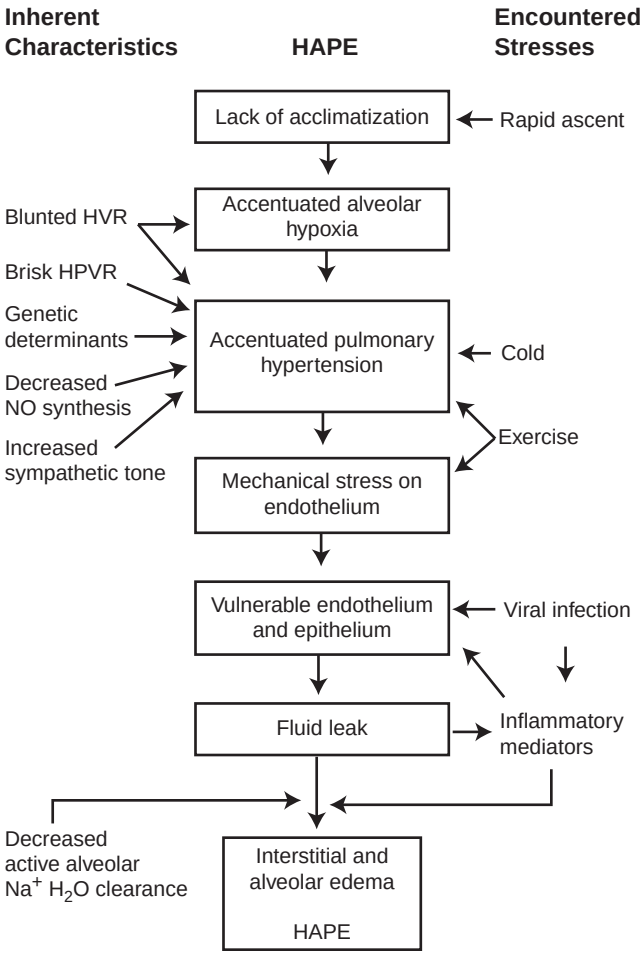


Fig. 25-1. Proposed pathophysiology of high-altitude pulmonary edema (HAPE). Interaction of the magnitude of ascent-induced hypoxia with other stresses and inherent characteristics of the individual cause accentuated pulmonary hypertension. Mechanical stress from the exaggerated increase in pulmonary vascular pressure increases normally low rate of fluid leak into the interstitial space. Increased fluid leak has both a hydrostatic component from pressure gradient and a permeability component from vascular endothelial disruption. Inflammatory mediators generated by hypoxia and tissue damage further exaggerate the permeability fluid leak. Build-up of fluid in the interstitial space and disruption of bronchial-alveolar epithelium causes alveolar flooding. Decreased sodium and fluid clearance by dysfunctional epithelium may also contribute to the abnormal fluid accumulation. Adapted with permission from Schoene RB, Swenson EK, Hultgren HN. High-altitude pulmonary edema. In: Hornbein TF, Schoene RB, eds. *High Altitude, An Exploration of Human Adaptation.* New York, NY: Marcel Dekker; 2001; 779.

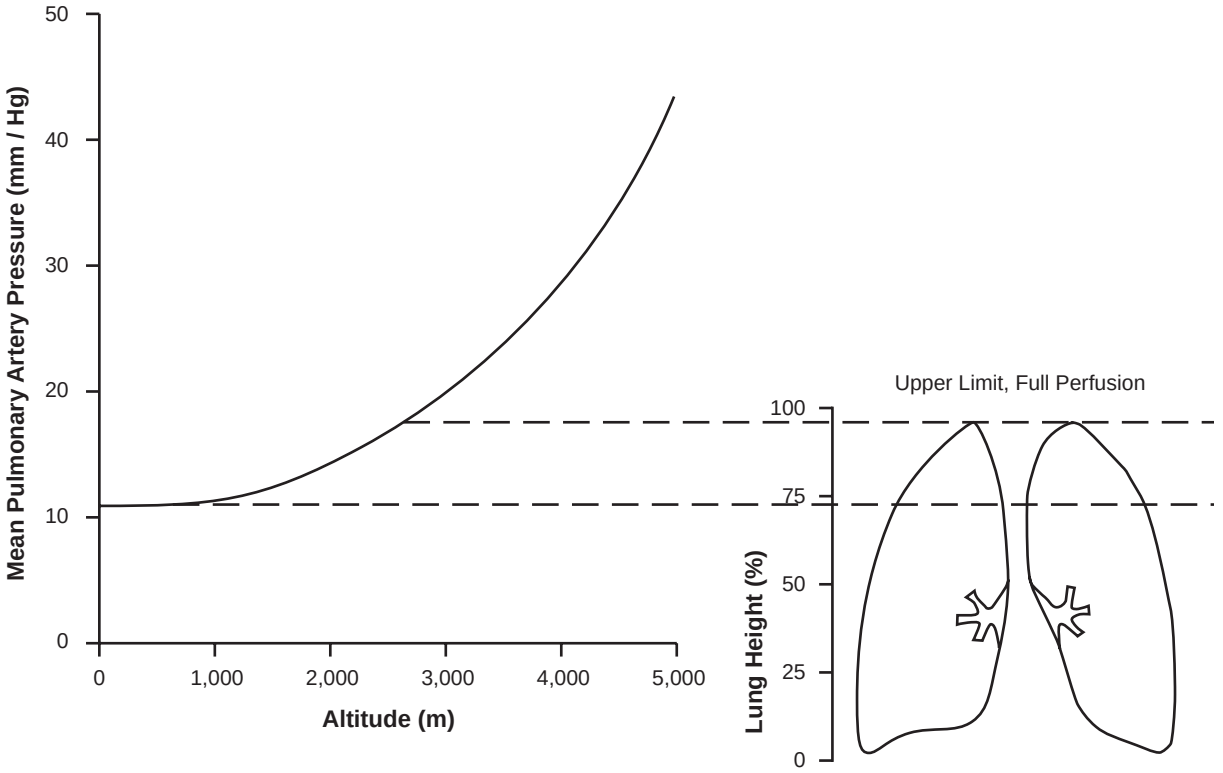


Fig. 25-2. Effect of altitude on mean pulmonary artery pressure measured in relation to lung hilum. Note that from sea level to 1,000 m (3,280 ft) in an erect body position, only the lower 70% of the lungs are continuously perfused (the upper lungs are perfused only during the systolic pulse). At an elevation of about 2,500 m (8,200 ft), the hypoxia-induced increase in mean pulmonary artery pressure allows continuous perfusion of the total lungs. Above 2,500 m, there is progressive pulmonary artery hypertension. Adapted with permission from Lenfant C, Sullivan K. Adaptation to high altitude. *N Engl J Med*. 1971;284:1303.

endothelial-derived nitric oxide when breathing a hypoxic gas mixture,[83] and populations indigenous to high altitude have high levels of exhaled nitric oxide, suggesting high production in their lungs, relative to low-altitude populations.[84] Additionally, inhaled nitric oxide has been shown to significantly reduce increased PAP and improve arterial oxygenation in HAPE-S subjects at high altitude.[85] Finally, the observation that HAPE-S individuals frequently have a smaller lung volumes compared with mountaineers who seem not to experience HAPE[70,79] caused Eldridge and colleagues[70] to speculate that a smaller pulmonary vascular bed in HAPE-S individuals might contribute to their exaggerated HPVRs.

Overperfusion of Pulmonary Vessels

The location of the fluid leak caused by hypoxia-induced pulmonary vasoconstriction is not known. For instance, the pulmonary vasoconstriction in HAPE may initially be heterogeneous and unevenly distributed, as suggested by the asymmetric distribution of rales and infiltrates seen on physical and radiographic examinations performed early in the course of the edema. Vessels that are not constricted are subjected to high pressures and flow and are relatively "overperfused," compared with vessels that are protected by the HPVR,[20,86] and the areas upstream from the constriction may also have very high intravascular pressures. The increase in hydrostatic forces in these overperfused areas can then lead to transudation of fluid into the alveoli, and edema may form in the interstitial spaces around the extraalveolar vessels proximal to the vasoconstriction. By the "classic" definition, if the edema in HAPE were caused only by an increase in hydrostatic forces, then it would be expected to have a low protein content.[87] The protein-rich nature of the lavage fluid and low capillary wedge pressure characteristically found in HAPE suggest that the edema is of the high-permeability variety, which could be secondary to very high pressures and flow that break down the pulmonary capillary endothelium.

Hackett and colleagues[88] reported four cases of

unilateral (left-sided) HAPE occurring at moderate altitudes (2,000–3,000 m [6,562–9,843 ft]) in adult patients whose right pulmonary artery was absent, and Rios and colleagues[89] reported a similar case in a 10-year-old child who also lacked a right pulmonary artery. Unilateral HAPE at moderate altitude has also been reported in a man with a hypoplastic right pulmonary artery[90] and in another with occlusion of the right pulmonary artery by calcified lymph nodes associated with granulomatous mediastinitis.[91] In these settings, all of the cardiac output (C.O.) is directed to one lung. The presumption is that as the individuals became more hypoxic, C.O. (and PAP) increased and led to exceedingly high pressures and flows in the vulnerable lung and the subsequent development of edema. HAPE has also been reported in association with pulmonary thromboembolism[92] and partial anomalous pulmonary venous drainage without an atrial septal defect.[93] (A similar situation is seen in individuals who have had pneumonectomy and develop pulmonary edema during exercise.[94]) These cases provide further indirect evidence of the importance of overperfusion of the pulmonary vascular bed in the pathophysiology of HAPE.

Stress Failure in the Pulmonary Circuit

West and colleagues[95–97] have shown that pulmonary capillaries that are exposed to high pressures may experience damage to the vascular endothelium and widening of the pores between endothelial membranes of adjacent cells, which can lead to high molecular weight proteins and red blood cells leaking into the interstitial and alveolar spaces. This concept, termed "stress failure" of the pulmonary capillaries, could explain the seemingly paradoxical finding of an edema caused by regional overperfusion, which should be transudative in nature, instead being characterized by high protein content in the alveolar fluid, a condition more suggestive of a high-permeability leak (see Figure 25-1). In an animal model, the integrity of the capillary membrane has been shown to be restored within minutes following a reduction in pressure.[98] Although this has yet to be proven in humans, it may explain why patients with HAPE often respond quickly to treatment with oxygen and other treatments aimed at lowering PAP (see the section on Treatment and Prevention, below).

Role of Exercise and Cold Exposure

Several of the early descriptions of HAPE,[10–12,49] as well as more-recent reviews,[13,17,22,77] state that vigorous exercise, exposure to the cold, or both, may be risk factors associated with the development of HAPE or may exacerbate the condition. This suggestion has yet to be demonstrated unequivocally, but there is good reason to believe that exercise and cold exposure may predispose to HAPE because they increase blood flow and pressure in pulmonary circulation.

The earliest evidence that exercise might contribute to increased PAP at altitude came in the 1960s, when Peñaloza and colleagues[99] found a greater increase in PAP during exercise at high altitude in individuals born and reared there than in sea-level residents exercising at sea level. Later, Wagner and colleagues[100,101] measured C.O. and PAP in eight normal subjects at rest and during exercise at sea level and simulated altitudes of 3,048 m (10,000 ft; PB 523 mm Hg) and 4,572 m (15,000 ft; PB 429 mm Hg). Their work demonstrates that (*a*) at all altitudes tested, PAP and C.O. increase with exercise intensity, and (*b*) for a given workload, PAP and C.O. are progressively elevated at higher altitudes, compared with sea level (Figure 25-3). Hultgren and colleagues[45] found a similar rise in the PAP of HAPE-S subjects exercising at altitude. More telling, perhaps, is that HAPE-S subjects have been shown to have a greater rise in PAP during exercise at sea level than normal control subjects,[50,71] and Eldridge and colleagues[70] found that during exercise at high altitude, HAPE-S subjects also have a greater rise in PAP than normal controls. Thus, pulmonary blood pressure and flow increase during exercise, and theoretically can lead to further overperfusion and stress on the pulmonary capillary wall, especially in HAPE-S individuals, predisposing to the development of edema. Although demonstration of a direct connection between the exercise-induced increase in PAP and HAPE has not been reported, Anholm and colleagues[102] have reported a prospective study in which they found radiographic evidence for early pulmonary edema in 33 elite bicycle racers following prolonged intensive exercise at 2,097 to 3,121 m (6,880–10,240 ft) altitude.

As does exercise, cold exposure increases PAP. Exposure to the cold has been shown to cause a significant increase in PAP in cattle,[103] rats,[104] and sheep.[105] The latter study further demonstrated that during exposure to cold ambient temperature (3°C) or hypoxia (F_{IO_2} = 11%), the rise in PAP was 24% and 27%, respectively. When the sheep were exposed to both hypoxia and cold simultaneously, the rise in PAP was greater (61%) than the sum of the two separate conditions, illustrating the independent (and perhaps synergistic) effects of cold exposure and hypoxia on the pulmonary vasculature.

Reeves and colleagues[106] reported epidemiological data that suggest the incidence of HAPE in human visitors to Summit County, Colorado (2,650–2,950 m [8,700–9,700 ft]), may be affected by cold conditions. In the only direct study reported on the effect of cold on PAP in humans, Hasen Nuri, Ali

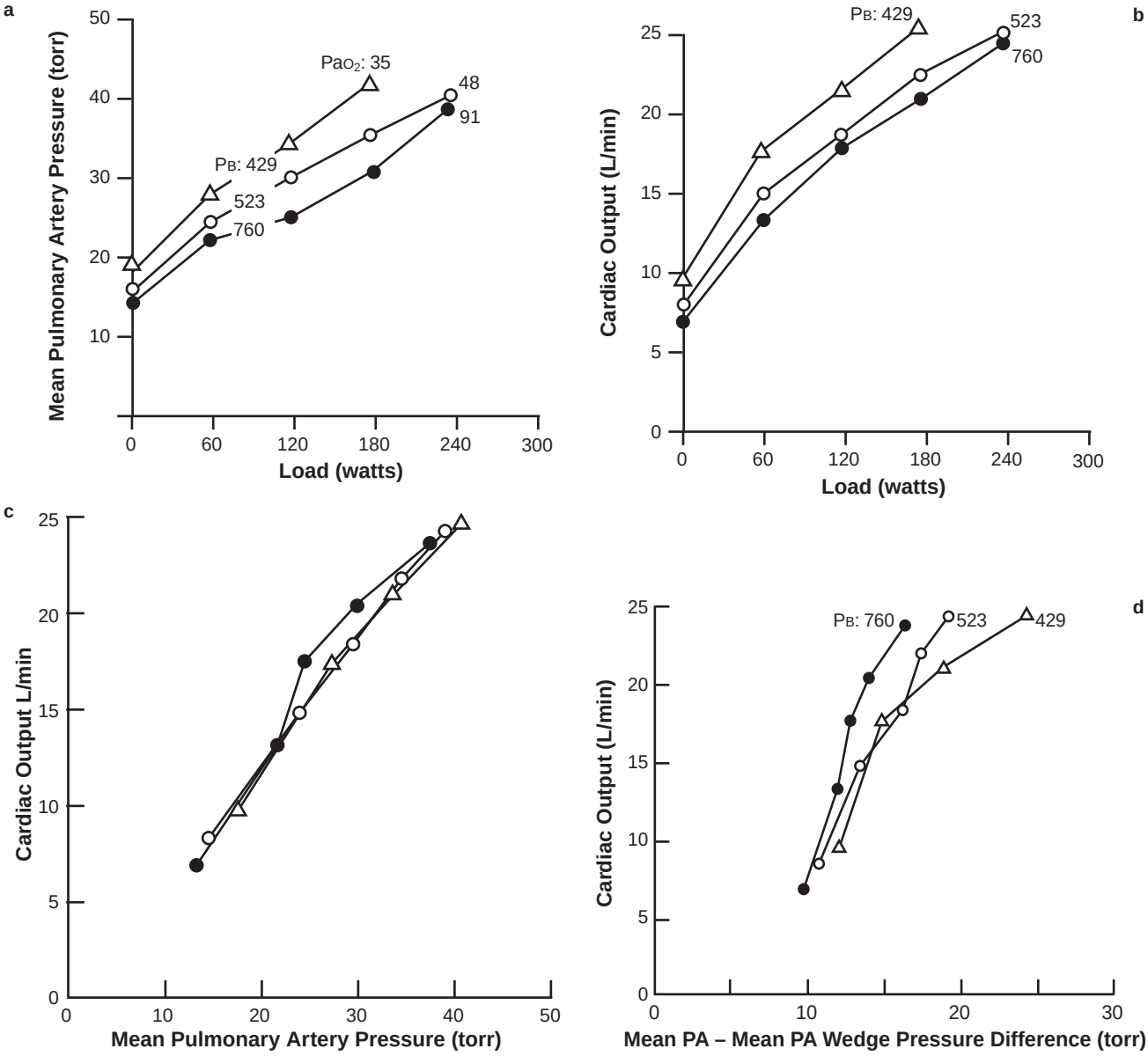


Fig. 25-3. Pulmonary hemodynamics during acute exposure to hypobaric hypoxia. Data represent mean values obtained by pulmonary artery catheter in eight normal volunteer subjects at rest and during three and four exercise (bicycle ergometer) work loads (in watts) at sea level (SL), 523 mm Hg (3,050 m/10,000 ft) and 429 mm Hg (4,574 m/15,000 ft) in a hypobaric chamber. Mean arterial oxygen (Pa_{O_2}) values at rest and during peak exercise at each simulated altitude were 95 and 91 mm Hg at SL; 56 and 48 mm Hg at P_B = 523 torr; and 39 and 35 mm Hg at P_B = 429 torr. (**a, b, c**) The panels show a parallel increase in mean pulmonary artery pressure (PAP_{mean}, mm Hg) and cardiac output (ie, blood flow; L/min) with increasing altitude and work level. (**d**) The panel shows increased pulmonary vascular resistance (PAP_{mean} – mean pulmonary capillary wedge pressure [$PCWP_{mean}$], mm Hg) with both altitude and higher work load. • = 760 mm Hg, ◦ = 523 mm Hg, Δ = 429 mm Hg. Reproduced with permission from Wagner PD. Hypobaric effects on the pulmonary circulation and high altitude pulmonary edema. In: Weir EK, Reeves JT, eds. *Pulmonary Vascular Physiology and Pathophysiology.* Vol 38. In: Lenfant C, ed. *The Lung in Health and Disease.* New York, NY: Marcel Dekker; 1989: 177–178.

Kahn, and Quraishi[107] evaluated the PAP response to a cold pressor test in a group of Indian soldiers and found a greater increase in PAP in HAPE-S subjects, compared with controls.

Role of Inflammation

The pathophysiology of HAPE is generally thought to be related to increased hydrostatic pressure within the pulmonary vasculature *in association with* increased endothelial permeability.[13,19,21,66,68,108,109] This so-called "hydrostatic permeability" hypothesis[21] suggests that the development of edema is accentuated by the simultaneous release of (*a*) vasoactive substances (leading to increased perfusion pressure) and (*b*) mediators that lead to increased endothelial permeability. Because the inflammatory process is mediated by substances that affect both blood flow and endothelial permeability, there has been much speculation as to a possible role of inflammation in HAPE.

Early evidence of an association of inflammation with HAPE came from autopsy findings that showed leukocyte infiltration and hyaline membranes in the alveoli of HAPE fatalities.[11,43,61,62,110] Results of epidemiological studies also support a possible role of inflammation in HAPE. A retrospective study of clinical records from children who developed HAPE at moderate altitudes in Colorado found that a preponderance of children with HAPE had a history of preexisting illness (most often upper respiratory infection), suggesting that the inflammation associated with their illness was a possible predisposing factor to developing HAPE.[111] Similarly, Hanaoka[112] and associates reported a greater number of the major histocompatibility-complex genotypes HLA-DR6 and HLA-DQ4 among adult HAPE-S individuals, compared with a normal population, a finding consistent with a possible genetic inflammatory predisposition.

The strongest evidence for inflammation's playing a role in HAPE stems from the findings of presence of inflammatory mediators in blood and BAL fluid of individuals with established HAPE and in HAPE-S and normal volunteer subjects exposed to high altitude. Richalet and colleagues[21] found an increase, followed by a decrease in the peripheral blood, of a number of eicosanoids, many of which play a role in inflammation, in normal volunteers during exposure to 4,350 m (13,998 ft) altitude. The time course and pattern of blood levels of specific eicosanoids that affect vasodilatation, vasoconstriction, or increasing permeability paralleled the time course of AMS. Elevated levels of urinary leukotriene E_4, a general marker of inflammation, were found to be increased in patients with HAPE seen in medical clinics in Summit County, Colorado (> 2,727 m [9,000 ft]), compared with patients without HAPE.[113] In addition to blood and urine, evidence for ongoing inflammation has been found on multiple occasions in BAL fluid from patients with HAPE.[34,55,56,58–60] Increased protein content and white blood cells, mostly alveolar macrophages and neutrophils, is a consistent finding in all BAL studies. Other findings include inflammatory eicosanoids,[55,56] cytokines,[58–60] and complement activation products.[55,56]

Although the evidence noted above certainly suggests that HAPE may be accompanied by inflammation, it does not answer the question of whether inflammation contributes to the initial vascular leak, because the data are either retrospective or were obtained from cases after the edema was well established. As such, these data do not provide very strong support for a role for inflammation in the onset of HAPE. Prospective studies have failed to demonstrate increase in inflammatory mediators prior to development of HAPE. For example, in a prospective study of HAPE-S subjects during 50 hours of altitude exposure (4,000 m [13,124 ft]) in a hypobaric chamber with exercise (30 min at 50% maximal oxygen uptake), Pavlicek and colleagues[114] found slight increase in acute-phase proteins C3 and α_1AT in peripheral blood but not in other acute-phase proteins or the vascular endothelial growth factor. None of the volunteer subjects developed HAPE, however. Kleger and colleagues[115] studied normal and HAPE-S subjects in the first 2 to 3 hours after they arrived at a research facility located on a mountain summit in the Swiss Alps at 4,559 m (14,958 ft). The researchers found only a modest increase in systemic albumin escape (a marker of vessel permeability) prior to development of HAPE in four of the volunteer subjects. After the onset of HAPE, proinflammatory cytokines and C-reactive protein increased in the peripheral blood. At the same location in the Swiss Alps, HAPE-S subjects had no increase in urinary leukotriene B_4 prior to developing HAPE but had an increase once HAPE was clinically apparent.[116] Finally, again at the same research location, Swenson and colleagues[117] performed BAL on HAPE-S subjects within hours of ascent and found protein in BAL fluid but no neutrophils or inflammatory cytokines. Considering all the evidence, most authorities believe that inflammation does not play a significant role in the onset of HAPE. This was conclusively demonstrated by Swenson and colleagues in 2002.[117b] That inflammation may play a later role in edema formation has not been excluded.[22]

Role of Hypoxic Ventilatory Response

The role of a reduced ventilatory response to hypoxia in the pathogenesis of altitude illness has previously been discussed. In general, people with a low hypoxic ventilatory response (HVR) are predisposed to developing AMS. This is presumably because the degree of hypoxia that develops at a given altitude in an individual is at least partially dependent on the HVR. If altitude illness is caused by the consequences of hypoxia, it is logical to expect that the incidence and prevalence of illness are proportional to the degree of hypoxia. Several studies have documented a similar relationship between a low HVR and susceptibility to developing HAPE.

In 1975, Lakshminarayan and Pierson[118] had the opportunity to study a young man who developed recurrent HAPE in the absence of any symptoms of respiratory distress and noted that his HVR was blunted. A few years later, Hyers and colleagues[119] exposed a group of HAPE-S subjects and controls to a simulated altitude of 4,150 m (13,616 ft) for 12 hours and found that relative to controls, the HAPE-S group developed more-pronounced hypoxemia associated with relative hypoventilation by 6 hours of exposure. The most convincing studies are those from Hackett and colleagues[120] (Figure 25-4), Matsuzawa and colleagues,[121] and Hohenhaus and colleagues[122]; these studies demonstrate that subjects susceptible to HAPE have a significantly lower HVR, compared with controls. However, these investigations also revealed that HAPE can develop in the presence of a normal HVR, and further that individuals with a low HVR do not necessarily develop HAPE. Cases have been reported in people with a high HVR as well.[123] Hackett and colleagues[120] concluded that a low HVR plays a permissive rather than a causative role in the pathogenesis of HAPE. Individuals with a low HVR and an exaggerated HPVR may be particularly prone to developing HAPE.[18] HAPE has frequently been reported to occur or to progress during the night. HAPE-S subjects have been reported to have irregular nocturnal breathing patterns,[124] but this abnormal breathing appears to be an effect, rather than a cause, of HAPE.[125]

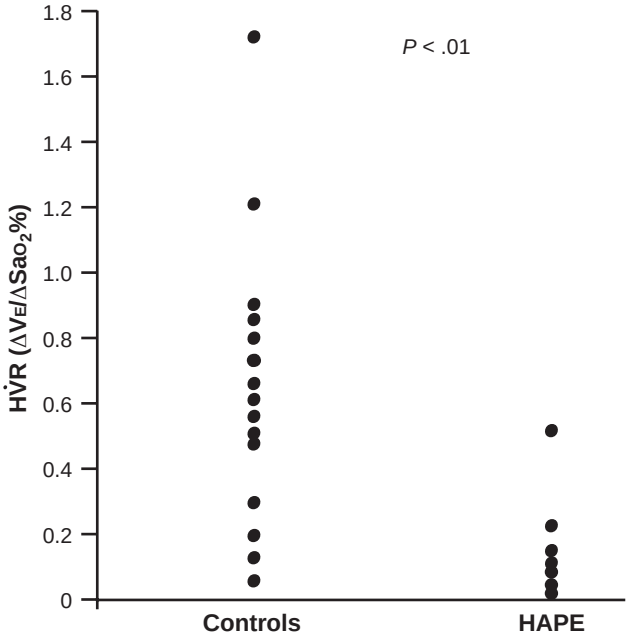


Fig. 25-4. Hypoxic ventilatory response (HVR) in 17 climbers without altitude illness (controls) and 7 climbers with high-altitude pulmonary edema (HAPE) measured at 4,400 m (14,436 ft) on Denali (Mount McKinley, Alaska). The mean value for the HAPE group was statistically significantly lower than that of the controls. The observation that some individuals in the control group had HVR values as low as individuals in the HAPE group yet did not experience HAPE suggests that a low HVR alone is not sufficient to cause HAPE. Adapted with permission from Hackett PH, Roach RC, Schoene RB, Harrison GL, Mills WJ Jr. Abnormal control of ventilation in high-altitude pulmonary edema. *J Appl Physiol*. 1988;64(3):1270.

Role of Fluid Alterations

The alterations in fluid homeostasis that occur during ascent to high altitude and the association between these changes and the development of AMS and HACE were reviewed in Chapter 24, Acute Mountain Sickness and High-Altitude Cerebral Edema. Bärtsch and colleagues[126] demonstrated that HAPE-S subjects develop fluid retention even during a relatively slow ascent to high altitude, and also that this alteration in fluid balance was associated with a widening of the right atrium and an increase in atrial natriuretic peptide (ANP).

Several other studies have documented that ANP levels are elevated in HAPE subjects,[127–129] as well as subjects with a history of HAPE who were then subjected to an acute hypoxic stress.[130] ANP levels correlate with the cross-sectional dimension of the right atrium as measured by echocardiography,[126] as well as the degree of elevation of PAP.[130] It has been speculated that ANP levels are elevated in HAPE subjects as a result of right atrial stretching caused by elevated PAP, fluid retention, and centralization of blood volume.[126] But it is unclear

whether elevated ANP levels contribute to the development of edema in HAPE, or whether this finding is simply an epiphenomenon.

Role of Alveolar Fluid Clearance

Accumulation of edema fluid in the pulmonary interstitial spaces and alveoli is not only a function of the rate at which fluid leaves the vasculature but is also dependent on how fast the extravasated fluid is cleared.[131] Findings consistent with decreased epithelial handling of sodium in the respiratory epithelium of HAPE-S, compared with HAPE-resistant subjects, suggest that individuals susceptible to HAPE may have a genetic impairment of their ability to clear edema fluid from their lungs.[132] Scherrer and colleagues[133] suggest that the combination of high PAP from an exaggerated HPVR and decreased alveolar fluid clearance may help explain differences between individuals in HAPE susceptibility.

TREATMENT AND PREVENTION

Although the treatment of HAPE depends to some degree on the severity of illness, descent is *always* an effective treatment.[4,13,17,18,66,109,134] Unfortunately, descending may not always be feasible owing to extreme weather conditions, concomitant trauma, or the tactical situation. Descent is not always necessary in cases of mild or moderate HAPE if bed rest, oxygen, and patient observation are available. For example, in many recreation sites (ie, ski areas), patients with HAPE may present with mild-to-moderate disease. If the patients' blood oxygen saturation can be improved with low-flow oxygen to 90% or greater and if they can be observed at night by family or friends, then it is reasonable to send the patients to their accommodations overnight and see them again the next day. Hultgren[23] presented a classification of HAPE severity based on the patient's specific signs and symptoms and electrocardiographic and chest radiographic findings, and suggested that patients with Grades 1 and 2 (mild and moderate, respectively) HAPE could often be treated with bed rest alone. This approach of bed rest and the initiation of oxygen therapy at 4 to 8 L/min by nasal cannula or mask will lead to a dramatic improvement in symptoms within 2 to 6 hours,[11] and complete recovery and resolution of pulmonary edema over the next few days.[31,42]

Mortality has been reported[16] to be as high as 44% in one case series of 166 patients when descent was impossible and supplemental oxygen was unavailable. This situation is not an unusual one for mountaineers to encounter, and so it is obvious that a search for other effective therapeutic options is warranted. Several pharmacological and nonpharmacological modalities directed at improving oxygen tension, lowering PAP, or both have been evaluated in the treatment of HAPE. Given the low incidence of the disease, studying these various modalities in a prospective, randomized, placebo-controlled fashion is very difficult. Despite these limitations, however, several recommendations can be made based on information available in the literature.

Nonpharmacological Modalities

Several nonpharmacological approaches have been evaluated, recommended, or both as potential HAPE therapies when descent is not possible. These include bed rest alone, expiratory positive airway pressure (EPAP), and simulated descent using a portable hyperbaric chamber (see Figure 24-9 [b] in Chapter 24, Acute Mountain Sickness and High-Altitude Cerebral Edema). Marticorena and Hultgren[36] studied 36 children and young adults who developed HAPE of mild-to-moderate severity at an altitude of 3,750 m (12,303 ft). Sixteen subjects were treated with bed rest alone, and 20 subjects received "traditional" treatment including continuous administration of oxygen (6–12 L/min) and bed rest. Although oxygen therapy resulted in quicker resolution of symptoms and greater reductions in heart rate, all subjects treated with bed rest alone fully recovered. Furthermore, the average length of stay in the hospital was similar in both groups. The authors concluded that HAPE of mild-to-moderate severity that develops at relatively low altitude can be treated with bed rest alone, but that this should not be substituted for descent, supplemental oxygen, or both, if feasible and available.

The application of positive expiratory pressure was first proposed as an adjunctive treatment for HAPE in 1977; Feldman and Herndon's[135] rationale was that "positive airway pressure is an effective treatment for pulmonary oedema of any cause."[135(p1037)] The device that they described was cumbersome and untested in the mountainous setting and also impractical to bring on field expeditions; however, the advent of the Downs mask—a lightweight, portable mask developed for use in nonintubated hospital patients—made it possible to study this concept in HAPE. Two uncontrolled studies, with a total of seven patients with HAPE, have demonstrated that the application of EPAP at 5 to 10 cm H_2O pressure for several minutes leads to increased Sa_{O_2}.[136,137] The

mask was well tolerated and did not lead to any obvious adverse effects; however, in subjects who wore the mask for several hours, symptoms and signs of HAPE returned shortly after the masks were removed. In addition, the application of EPAP at higher levels (> 10–15 cm H_2O) may cause barotrauma or lead to a decreased C.O. A case of HACE believed to be caused by using positive end-expiratory pressure (PEEP) as a treatment for HAPE has also been reported.[138] EPAP may be useful as a temporizing measure until descent is possible, but more experience is needed before it can be widely recommended.

Another nonpharmacological modality that has been employed in the treatment of HAPE is the portable hyperbaric chamber (PHC). The rationale for its use in other forms of altitude illness has been discussed in Chapter 24, Acute Mountain Sickness and High-Altitude Cerebral Edema. The PHC has been used in several patients with HAPE and has been reported to be very effective, but these reports are descriptive in nature and uncontrolled, and often the patients were receiving other concurrent therapies; thus, the independent beneficial contribution of the PHC was difficult to ascertain.[139,140] Theoretically, the PHC should be as useful as supplemental oxygen because both of these interventions work by increasing arterial oxygen tension (Pa_{O_2}). It is often impractical to carry heavy metal tanks of oxygen on an expedition; the few groups that bring oxygen usually only carry a single bottle.[141] As a consequence, the supply of oxygen in the field is usually limited. The PHC offers the advantage of being lightweight and more easily transportable, and it can be used repeatedly and for long periods of time.

Hackett[142] compared the effect of supplemental oxygen with the PHC in nine individuals who developed HAPE on Mount McKinley (at an altitude of 4,300 m [14,108 ft]). Alveolar oxygen tensions (P_{AO_2}) were matched during both treatments, and symptomatic improvement was similar in both groups. The authors of another study,[143] the primary focus of which was to compare the effect of the PHC versus supplemental oxygen in AMS, concluded that simulated descent with the PHC and supplemental oxygen were equally effective for relieving symptoms of AMS. This study included six people with coexisting "mild" HAPE; analysis of the data in this subset yielded similar results.

Although patients with HAPE may have difficulty tolerating the recumbent position necessary for optimal use of the PHC,[144] it is an effective temporizing measure for the treatment of HAPE and may be lifesaving in instances where descent is impossible and oxygen is not available. Additionally, most PHC devices are sufficiently lightweight and portable so that they can be positioned at a sloping angle, with the head of the enclosed patient higher than the feet. Areas of further research should focus on the optimal duration of treatment, the incidence of recurrence of disease after treatment, and the potential synergistic effects of pressurization and supplemental oxygen.

Vigorous coughing in the head-down position accompanied by steady pressure applied to the upper abdomen has been reported to be effective in facilitating drainage of edema fluid and temporarily improving symptoms.[145] Other, more-general, treatment considerations include minimizing exertion and keeping the victims warm (and having them breathe warmed air if possible), as exercise and exposure to cold may lead to an increase in PAP.

Pharmacological Modalities

Historically, a wide variety of drugs such as antibiotics, corticosteroids, digitalis, morphine, atropine, aminophylline, and diuretics have been utilized in the treatment of HAPE[11,12,27,31,42,67]; however, controlled studies evaluating the effectiveness of any of these therapies have not been performed. As more is understood about the pathophysiology of HAPE, it is clear that little rationale exists for the indiscriminate use of antibiotics, digitalis preparations, aminophylline, atropine, or corticosteroids. Given that HAPE is noncardiogenic and that patients are often intravascularly volume-depleted, it is also possible that treatment with diuretics (and perhaps morphine) may have a detrimental effect.

Although comparative investigations have not been performed, Scoggin and colleagues[27] stated that in a group of 39 people with HAPE, "there were no differences in response between oxygen treatment alone (n = 8) and oxygen combined with drugs"[27(p1271)] (ie, some combination of antibiotics, corticosteroids, and diuretics). In another study[26] of 32 patients with HAPE, all of whom were treated with supplemental oxygen, 20 received furosemide; this group had a longer mean hospital stay compared with the group treated only with oxygen. Gray and colleagues,[146] in a study indirectly evaluating the effect of acetazolamide and furosemide on AMS, noted that "subjects started on furosemide on arrival at altitude quickly became medical casualties,"[146(p84)] and concluded that "[p]owerful diuretics such as furosemide ... in fact may be dangerous at high altitude."[116(p84)] In 1962, Hultgren, Spickard, and

Lopez[42] were originally in favor of using diuretics; however, in 1975, Hultgren[147] commented on the considerable risks associated with the use of furosemide in HAPE and pointed out that there was insufficient evidence to justify its use.

Recent reviews of HAPE[4,6,13,17,109,134] generally suggest that (*a*) there are no data to substantiate the use of diuretics, morphine, or both in HAPE, and their use remains controversial; (*b*) diuretics and morphine are not useful in treating HAPE in the field because of the potential adverse effects; or (*c*) when used, diuretics and morphine should only be given in situations where blood pressure and fluid status can be closely monitored.

Another medication that has been suggested for use in the prevention and treatment of HAPE is acetazolamide because it has proven efficacy in AMS; however, supportive data from controlled studies are not available. Acetazolamide reduces symptoms and prevents further impairment of pulmonary gas exchange in AMS subjects,[148] improves Sa_{O_2} and reduces periodic breathing during sleep at high altitude,[149,150] and is effective in the prophylaxis of AMS.[151] In the latter study, it was noted that vital capacities were increased in the acetazolamide-treated group at high altitude, and Larson and colleagues[151] surmised that these climbers developed less interstitial edema in the lung. They further speculated that if this was true, "acetazolamide could diminish the incidence and severity of HAPE"[151(p332)] and also "could prove effective in preventing HAPE, as well as improving performance at altitude."[151(p332)] Hackett and colleagues,[35] while participating in the Denali Medical Research Project on Mount McKinley from 1982 to 1985, had the opportunity to treat many HAPE victims. Acetazolamide, in their opinion, "seemed to be beneficial when given early in the course of the illness."[35] They also remarked that HAPE responded so well to supplemental oxygen and descent that no one needed to be evacuated, and except for acetazolamide, no other medications were administered. Because nifedipine, a calcium channel–blocking agent, became the standard pharmacological adjunct to both prevent and treat HAPE during the 1990s and early 2000s[17,24,25] (see below), the long-standing debate on whether diuretics, morphine, and acetazolamide are indicated in the management of this disease may well be obsolete.

A mountaineer who was also a physician and scientist interested in altitude physiology and medicine (Oswald Oelz) developed HAPE in 1986 while ascending Mount Makalu in Nepal. He treated himself with 20 mg of nifedipine sublingually, and noted that within 15 minutes his dyspnea improved and sputum production decreased.[152,153] He took 20 mg of a slow-release preparation periodically and additional sublingual doses as needed until he had descended safely. His experience prompted further interest in examining the effect of nifedipine in patients with HAPE. Dr Oelz studied 6 male subjects who developed clinical and radiographic evidence of HAPE while ascending Monte Rosa, an Alpine peak between Italy and Switzerland (on which a research laboratory is located at 4,559 m [14,958 ft]). Oelz and colleagues[53] found that treating these subjects with 10 mg of nifedipine sublingually followed by 20 mg of a slow-release preparation every 6 hours led to an improvement in symptoms, usually within 15 to 30 minutes after the first sublingual dose. Nifedipine was postulated to be effective because it reduced PAP (measured by doppler echocardiography) to values approaching that of controls, thereby reducing the hydrostatic forces that lead to the transudation of fluid into the alveoli.

In a prospective, randomized, placebo-controlled, double-blind study, Bärtsch and colleagues[29] proved in 1991, in a group of subjects who had a previous history of HAPE, that nifedipine is effective in decreasing PAP and preventing the development of HAPE. In 1994, these same researchers[154] found that nifedipine was not effective in preventing AMS symptoms in subjects who were not HAPE-susceptible; they believed that its use in high-altitude medicine should be limited to preventing HAPE in susceptible subjects and treating HAPE when immediate descent is not possible and supplemental oxygen is not available.

Hackett and colleagues[54] compared the effects of oxygen, nifedipine, hydralazine, phentolamine, and a combination of oxygen and phentolamine on the pulmonary vasculature in HAPE subjects. All of the vasodilators studied decreased pulmonary vascular resistance and mean PAP to varying degrees and improved gas exchange (Figure 25-5), thus providing more indirect evidence that pulmonary vasoconstriction is associated with edema formation. It is interesting to note that the α-adrenergic blocking agent phentolamine caused the greatest reduction in these parameters and also had an additive effect when combined with oxygen therapy, implying that the sympathetic nervous system may be involved in the pathophysiology of HAPE. Controlled studies evaluating the therapeutic benefit of these other agents are warranted; however, they cannot be recommended for use at this time.

In summary, although some of the pharmacological (particularly nifedipine) and nonpharmacological

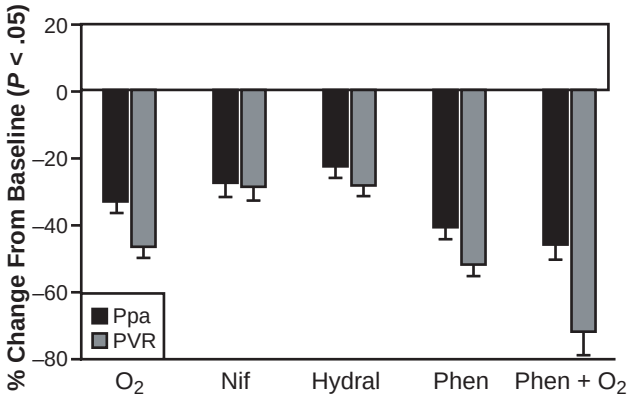


Fig. 25-5. The percentage change in mean pulmonary artery pressure (Ppa) and pulmonary vascular resistance (PVR) with five different interventions (see key to graph, below) in a total of 16 patients with high-altitude pulmonary edema (HAPE) and 6 controls. Data are pooled from three data-collection periods, and some individuals must have been included in more than one category (eg, the 10 persons in the first two cagetories apparently received oxygen first and then nifedipine). All changes in Ppa and PVR from baseline were significant ($P < .05$) for all interventions. For Ppa reduction, phentolamine was statistically more effective than either oxygen or hydralazine. Oxygen with phentolamine was more effective than phentolamine alone. For PVR reduction, oxygen and phentolamine were more effective than hydralazine. Phentolamine and phentolamine with oxygen were more effective than nifedipine. Reproduced with permission from Hackett PH, Roach RC, Hartig GS, Greene ER, Levine BD. The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: A comparison. *Int J Sports Med*. 1992;13 suppl 1:S69.
O_2: oxygen (n=10); Nif: nifedipine (n=10); Hydral: hydralazine (n=3); Phen: phentolamine (n=6); Phen+O_2: phentolamine and oxygen (n=6).

modalities (particularly the PHC) discussed may be appropriate as temporizing or prophylactic measures in specific circumstances, they should not be utilized in place of either standard prevention measures (ie, acclimatization and slow ascent) or treatment strategies (ie, descent, supplemental oxygen).

SUMMARY

HAPE is a is a noncardiogenic pulmonary edema that occurs in unacclimatized individuals who ascend rapidly from low altitude to altitudes usually over 2,500 m (8,203 ft) and remain there for more than a few hours. Because HAPE can rapidly be fatal, it is a serious threat to military personnel who may be required to ascend rapidly into high mountains as a contingency of their mission. The pathophysiological mechanisms that cause HAPE are not precisely defined, but they appear to involve an exaggerated hypoxia-induced increase in pulmonary blood pressure, which may cause overperfusion of parts of the pulmonary circuit and stress failure of capillaries with subsequent leak of fluid, protein, and cells into the interstitial tissue and alveoli of the lungs. Hypoxia-induced decrease of alveolar epithelial sodium pump function may limit fluid clearance and contribute to the edema. The leak of fluid and cells may trigger an inflammatory reaction that also contributes to the edema. Some individuals seem much more susceptible to HAPE than others, suggesting that a component of genetic predisposition may be present in the pathophysiology.

HAPE is characterized by a persistent cough that progresses to a production of a pink-tinged or blood-flecked sputum; inappropriate dyspnea with exertion that progresses to dyspnea at rest; and lethargy and fatigue that progresses to confusion, decreased consciousness, and coma.

Untreated HAPE can rapidly be fatal. Descent to a lower altitude is the mainstay of treatment in HAPE, and immediate descent often results in rapid and complete recovery. Descent of as few as 300 m (~1,000 ft) can be lifesaving in some instances. Accepted adjunctive therapies for HAPE include supplemental oxygen and the calcium-channel antagonist nifedipine. HAPE can often be prevented by slow ascent, which allows the body to acclimatize to hypoxia, and by nifedipine taken prophylactically.

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