There are two typical settings for HAPE, a pulmonary oedema which may occur in healthy individuals within a few days of arrival at high altitude. The first setting involves high-altitude dwellers returning from sojourns at low altitude, while the second involves rapid ascent by unacclimatised lowlanders. The first medical description of HAPE was published in Peru and recognised reentry HAPE as a pulmonary oedema associated with electrocardiographic signs of right-ventricular overload [1]. The first cases of HAPE in unacclimatised lowlanders climbing to high altitude were reported from the Rocky Mountains [2]. The two forms very probably share the same pathophysiology.

Altitude, rate of ascent and, most importantly, individual susceptibility are the major determinants for the occurrence of high altitude pulmonary oedema (HAPE). This illness usually develops only within the first 2–5 days after acute exposure to altitudes above 2500–3000 m. An excessive rise in pulmonary artery pressure preceding oedema formation is the crucial pathophysiological factor. Recent investigations using right heart catheterisation and bronchoalveolar lavage (BAL) in incipient pulmonary oedema have shown that HAPE is a hydrostatic oedema in the presence of normal left atrial pressure with non-inflammatory high permeability leakage of the alveolocapillary barrier and mild alveolar haemorrhage. An inflammatory response may develop later in more advanced cases, as has been documented by BAL. Furthermore, decreased fluid clearance from the alveoli may contribute to such non-cardiogenic pulmonary oedema. Supplemental oxygen is the primary treatment in areas with medical facilities, while the treatment of choice in remote mountain areas is immediate descent. When this is impossible and supplemental oxygen is not available, treatment with nifedipine is recommended until descent is possible. Even susceptible individuals can avoid HAPE if they ascend slowly with an average gain of altitude not exceeding 300–350 m/day above an altitude of 2500 m.

**Epidemiology**

There are two typical settings for HAPE, a pulmonary oedema which may occur in healthy individuals within a few days of arrival at high altitude. The first setting involves high-altitude dwellers returning from sojourns at low altitude, while the second involves rapid ascent by unacclimatised lowlanders. The first medical description of HAPE was published in Peru and recognised reentry HAPE as a pulmonary oedema associated with electrocardiographic signs of right-ventricular overload [1]. The first cases of HAPE in unacclimatised lowlanders climbing to high altitude were reported from the Rocky Mountains [2]. The two forms very probably share the same pathophysiology.

Altitude, rate of ascent and, most importantly, individual susceptibility are the major determinants of HAPE in mountaineers and trekkers. The prevalence of HAPE is <0.2% in a general alpine mountaineering population when ascent occurs in three or more days to an altitude of 4559 m. When the same altitude is reached within 22 hours, the incidence increases to 7% in mountaineers without, and to 62% in those with, a history of radio-graphically documented HAPE [3]. The incidence of HAPE also increases from 2.5 to 15.5% when an altitude of 5500 m is reached by airlift [4] as opposed to trekking over 4–6 days [5].

HAPE may also occur at lower altitudes between 2500 and 3000 m in the Japanese Alps and in North America [6]. The estimated incidence in visitors to ski resorts in the Rocky Mountains of Colorado is 0.01–0.1% [7]. Women may be less susceptible to HAPE than men [8, 9]. Re-entry HAPE has also been reported from the Rocky Mountains and appears to run in susceptible families and chiefly affect children, findings also reported from the Andes [10, 11].

Most recently HAPE has been reported in Alpine resorts located at altitudes between 1400 and 2400 m in an area with facilities for skiing up to 3200 m [12]. Susceptibility to HAPE may have been increased in these patients by previous or unrecognised underlying illness, as discussed later in this review, and some may have had diastolic heart failure rather than HAPE, due to hypertensive heart disease.
Signs and symptoms

HAPE presents within 2–5 days of arrival at high altitude [4]. It is rarely observed below altitudes of 2500–3000 m and after 1 week of acclimatisation at a particular altitude. In most cases it is preceded by symptoms of acute mountain sickness (AMS) [13]. Early symptoms of HAPE include exertional dyspnoea, cough and reduced exercise performance. As pulmonary oedema progresses, cough worsens and breathlessness at rest and sometimes orthopnoea occur. Gurgling in the chest and pink frothy sputum indicate advanced cases.

The clinical features are cyanosis, tachypnoea, tachycardia and elevated body temperature generally not exceeding 38.5 °C. Rales are discrete initially and typically located over the middle lung fields. There is often a discrepancy between the minor findings on auscultation compared with the degree of alveolar infiltration on chest x-ray. In advanced cases signs of concomitant cerebral oedema, such as ataxia and decreased levels of consciousness, are frequent findings.

Subclinical HAPE probably occurs and causes no or minimal symptoms which can be ignored or attributed to other factors. The true incidence is unknown, although two recent studies have suggested that upwards of 50% of persons may have subclinical fluid accumulation in the lung, consistent with occult oedema which resolves spontaneously even though subjects remain at high altitude [14, 15]. These studies employed very indirect measures of lung water changes, spirometry, closing volume and transthoracic impedance, all of which may vary for other reasons relating to the high altitude environment, such as increases in cardiac output, cold-induced mild bronchoconstriction, exercise and hypocapnia.

Further evaluation

Ordinarily there are no characteristic laboratory findings [6]. Abnormal results may be due to concomitant dehydration, stress and previous exercise. Inflammation markers and changes in blood coagulation are discussed in the section on pathophysiology. Arterial blood gas measurements in 4 cases of advanced HAPE at 4559 m demonstrate the severity of this illness; mean arterial PO$_2$ was 23 ± 3 (SD) mm Hg (controls: 40 ± 5) and arterial oxygen saturation was 48 ± 8% (controls 78 ± 7%) [16]. In early cases values around 30 mm Hg for PO$_2$ and 70% for SaO$_2$ are observed at this altitude.

Chest x-ray and CT-scans in early HAPE show patchy peripheral distribution of oedema, as shown in Figure 1. The radiographic appearance of HAPE is more homogeneous and diffuse in advanced cases and during recovery [17–19]. Moreover, in patients who had two episodes of HAPE the similarity of the radiographic appearance between the two episodes was random, suggesting that structural abnormalities do not account for oedema location [18].

Autopsies reveal distended pulmonary arteries and diffuse pulmonary oedema with bloody foamy fluid present in the airways but no evidence of left ventricular failure [20, 21]. Further, hyaline membranes were found in most cases and arteriolar thrombi, pulmonary haemorrhages or infarcts were often present.

Figure 1
Chest x-ray and CT of a male patient with recurrent HAPE showing patchy distribution of oedema, predominantly in the upper lung fields on the right side.
Pathophysiology

Haemodynamics

*Exaggerated pulmonary artery pressure*

Cardiac catheterisation of untreated cases of HAPE at high altitude reveals mean pulmonary artery pressures of 60 (range 33–117) mm Hg [22–24], while wedge pressures are normal. Estimations of systolic pulmonary artery pressure by echocardiography reveal values between 50 and 80 mmHg for subjects with HAPE and 30–50 mm Hg for healthy controls [25–27].

It is well established that an excessive rise in pulmonary artery pressure is crucial for the development of HAPE, since this pressure rise precedes HAPE [26] and drugs lowering pulmonary artery pressure improve gas exchange in HAPE [27, 28] and are effective in its treatment [29] and prevention [26]. Individuals susceptible to HAPE also exhibit an exaggerated pulmonary artery pressure rise under hypoxia and exercise [30–32].

At Capanna Margherita (4559 m) right heart catheterisation recently showed that the abnormal rise in pulmonary artery pressure in individuals susceptible to HAPE is accompanied, as shown in Figure 2, by capillary pressure increased to above 20 mm Hg in those who develop HAPE [33]. This threshold value is in keeping with previous experimental observations in dogs of a PO₂-independent critical capillary pressure of 17–24 mm Hg, above which the lungs continously gain weight [34]. These results suggest that pulmonary capillary hypertension plays an important role in the pathophysiology of HAPE.

*Mechanisms of exaggerated hypoxic pulmonary vascular response (HPVR)*

The cause of exaggerated HPVR in HAPE-susceptible subjects is not known. Besides a possibly increased pulmonary hypoxic vasoconstrictor response, a lower hypoxic ventilatory response (HVR) [35–38] and slightly lower lung volumes [37, 39, 40] may contribute to increased PAP by causing greater alveolar hypoxia [41] and reducing the number of recruitable vessels. Furthermore, microneurography in HAPE subjects demonstrates increased muscular sympathetic activity during hypoxia at low altitudes and prior to HAPE at high altitudes [42]. In accordance with these findings, increased plasma and/or urinary levels of...

Figure 2

Mean pulmonary artery pressure (Ppa) and pulmonary capillary pressure (Pcap) in 14 controls and in 16 high altitude oedema-susceptible (HAPE-s) subjects at high altitude. HAPE-s is further divided into those who developed HAPE (HAPE) and those who did not (non-HAPE). Bars indicate the mean values in each group. * p<0.05, ** p<0.01 vs. control, † p<0.01 vs. non-HAPE.

Figure 3

Left panel: Exhaled NO over 40 hours at 4559 m in individuals developing HAPE and not developing HAPE (HAPE-R) despite identical exposure to high altitude (data from [49]). Right panel: Exhaled NO in individuals with (HAPE-S) and without (HAPE-R) susceptibility to HAPE during 4 hours of exposure to hypoxia (FiO₂ = 0.12) at low altitude (data from [48]).
High altitude pulmonary oedema occurs during the first few days of acute exposure and accounts for the clinical observation that HAPE only affects the more homogeneous perfusion. Uneven distribution of pulmonary oedema rich in protein and red blood cells is consistent with right pulmonary artery remodelling. Rapid remodelling resulting in regional overperfusion of capillaries in areas of low hypoxic vasoconstriction causes susceptibility to HAPE in individuals with an abnormal pulmonary leak index. The observation of increased protein concentration in the BAL fluid of mountaineers with more advanced HAPE on Mount McKinley and in hospitalised HAPE patients in Japan shows elevated red blood cell counts and serum-derived protein concentration in the BAL fluid (see table) both in subjects with HAPE and in those who developed HAPE within the next 24 h. Although these findings are consistent with a possible inflammatory leak, there was no increase in alveolar macrophages and neutrophils or in the concentration of proinflammatory mediators (interleukin-1, TNF-alpha, IL-8, thromboxane, prostaglandin E2 and leukotriene B4) at high altitude, and there was no difference between individuals resistant and susceptible to HAPE. The fact that the alveolar protein concentration may exceed the plasma protein concentration in HAPE suggests that active salt and water reabsorption occurs and concentrates the protein leaked in the initial stages of HAPE (see discussion below on alveolar fluid clearance).

Inflammation BAL performed within a day of ascent to 4559 m reveals elevated red blood cell counts and serum-derived protein concentration in the BAL fluid (see table) both in subjects with HAPE and in those who developed HAPE within the next 24 h. Although these findings are consistent with a possible inflammatory leak, there was no increase in alveolar macrophages and neutrophils or in the concentration of proinflammatory mediators (interleukin-1, TNF-alpha, IL-8, thromboxane, prostaglandin E2 and leukotriene B4) at high altitude, and there was no difference between individuals resistant and susceptible to HAPE. The fact that the alveolar protein concentration may exceed the plasma protein concentration in HAPE suggests that active salt and water reabsorption occurs and concentrates the protein leaked in the initial stages of HAPE (see discussion below on alveolar fluid clearance).

These data indicate that there is a partial disruption of the alveolar-capillary barrier that is not caused by an inflammatory process. The intriguing finding of a normal pulmonary leak index in early HAPE, as reported by one of the authors, can be explained by the definition of this index, which uses a labelled protein to mark the magnitude of alveolar leak and labelled red blood cells as an indicator of the intra-vascular compartment. Since, in HAPE, red cells also leak into the alveoli, the leak cannot be detected by this method. However, analysis of bronchoalveolar lavage (BAL) fluid of mountaineers with more advanced HAPE on Mount McKinley and in hospitalised HAPE patients in Japan showed, in many but not all cases, not only high concentrations of proteins as measured in early HAPE,
but also elevated proinflammatory cytokines, leukotriene B4, and increased granulocytes. Furthermore, urinary leukotriene E4 excretion was increased in patients with HAPE reporting to clinics in the Rocky Mountains [65]. These observations suggest that, in more advanced cases of HAPE, inflammation may occur and contribute to enhanced pulmonary capillary permeability. Evidence of in-vivo thrombin and fibrin formation in advanced [16] but not in early HAPE or preceding HAPE [66] indicates that activation of blood coagulation only occurs in advanced cases and may be a consequence of the inflammatory response.

In conclusion, the results of all these studies indicate that HAPE is a hydrostatic type of pulmonary oedema, the pathophysiological mechanism of which is excessive hypoxic pulmonary vasoconstriction of small arteries and veins, probably leading to overdistension of the vessel wall, which opens the cellular junctions and possibly causes stress failure of the alveolo-capillary membrane [67]. Thus, signs of inflammation found in BAL fluid of patients with advanced HAPE are a secondary event.

It is conceivable that any process enhancing the permeability of the alveolar-capillary barrier would lower the pressure required to generate oedema. Indeed, increased fluid accumulation during hypoxic exposure after priming by endotoxins or viruses in animals [68] and the association of previous viral infections (predominantly of the upper respiratory tract) with HAPE in children visiting Colorado [69] support this concept. Under conditions of increased permeability HAPE may also occur in individuals with normal hypoxic pulmonary vascular response (Figure 4). Thus, upper respiratory tract infections shortly before a sojourn in the French Alps and vigorous exercise at altitudes between 2000 and 3000 m may explain why in some cases HAPE develops at a surprisingly low altitude [12]. Other cases may be due to diastolic heart failure in hypertension and to undiagnosed pathology favouring the occurrence of HAPE, such as silent pulmonary embolism possibly triggered by prolonged road, rail or air travel [70].

**Alveolar fluid clearance**

A further mechanism which may contribute to the pathophysiology of HAPE has been pointed out recently. Results obtained in cell cultures and animal models suggest that impairment of fluid clearance from the alveoli may be involved in the pathophysiology of HAPE. The cell and membrane processes which mediate water and sodium transport across type II alveolar epithelial cells are shown in Figure 5. Hypoxia decreases transepithelial sodium transport [71] and accounts for decreased fluid clearance from the alveoli of hypoxic rats at an FIO2 of 0.08 [72]. Mice partially deficient in the apical (alveolar-facing) epithelial sodium channel show greater accumulation of lung water in hypoxia [73]. Transalveolar sodium transport may be stimulated by beta-2 receptors and a recent field study has shown successful prevention of HAPE with inhalation of salmeterol, a beta-2 agonist [74]. It should, however, be noted that the doses employed were 2.5 times higher than recommended for the treatment of obstructive lung disease. Furthermore, due to the multiple actions of this drug, such as lowering of pulmonary artery

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**Table 1**

<table>
<thead>
<tr>
<th>BAL Fluid Composition</th>
<th>550 m</th>
<th>4559 m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONT</td>
<td>HAPE-S</td>
</tr>
<tr>
<td></td>
<td>n = 8</td>
<td>n = 9</td>
</tr>
<tr>
<td>White cell count (× 10⁶/ml)</td>
<td>8.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Red cells (% of total BAL cells)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total protein (mg/dl)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total protein (% of plasma protein)**</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>PAP systolic (mm Hg)</td>
<td>22</td>
<td>26</td>
</tr>
</tbody>
</table>

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**Figure 4**

Role of capillary pressure and inflammatory response in various forms of pulmonary leak. In early HAPE, increased intravascular pressure is the major factor accounting for oedema formation, while in advanced cases an inflammatory response contributes to oedema formation. In pneumonia or ARDS, intravascular pressure is, at least initially, normal in most cases and inflammation accounts for the leak. Increased permeability due to inflammation, such as an upper respiratory tract infection [69] or priming by endotoxins or viruses [68] prior to hypoxic exposure may facilitate the occurrence of pulmonary oedema in the presence of a normal increase in pulmonary artery pressure under hypoxia.
pressure, increasing of ventilatory response to hypoxia and tightening of cell-to-cell contacts, the contribution of stimulated alveolar fluid clearance to the positive study outcome is not clear [75]. With this consideration in mind, preliminary analysis of a subset of the patients of Sartori et al. [74] showed significant reduction of systolic pulmonary artery pressure by salmeterol [76]. Definitive evaluation of the role of depressed alveolar fluid clearance in the pathophysiology of HAPE will require more specific drugs.

Sartori et al. also found that HAPE-susceptible individuals had a lower transepithelial nasal potential in normoxia than non-susceptible controls [74], a reduction which could be ascribed to lower sodium transport by the epithelial sodium channel (ENaC). These findings may point to a constitutional, possibly genetically determined reduction of sodium transport across the respiratory epithelium. Although a recent investigation confirmed the difference in nasal potential between HAPE-susceptible individuals and controls in normoxia, this difference could not be attributed to the ENaC [77]. The study also showed that nasal epithelium may not adequately reflect ion transport across the alveolar epithelium. Hence the significance of a lower nasal potential in HAPE-susceptible individuals is unclear for the moment.

**Prevention**

Slow ascent is the most effective method of prevention, and one that is effective even in susceptible individuals. Personal observations of 9 ascents in 7 mountaineers (by P.B.), who had all developed HAPE more than once upon rapid ascent in the Alps, indicate that altitudes of up to 7000 m can be reached by these individuals without medical problems when the average daily ascent rate above 2000 m does not exceed 350–400 m per day or with a staged ascent [79].

To avoid life-threatening illness, mountaineers with symptoms of altitude sickness should be advised not to ascend further and to descend if the symptoms do not improve after a rest day. Since exercise-induced circulatory changes may worsen or cause pulmonary oedema [31], vigorous exercise should be avoided during the first days of altitude exposure by individuals with a history of HAPE and by those with symptoms of altitude sickness, or after a rapid ascent to altitudes above 3500–4000 m. As pointed out earlier, susceptibility to HAPE may be increased during and shortly after infections [69].

Prophylaxis with nifedipine (an inhibitor of hypoxic pulmonary vasoconstriction) can be recommended for individuals with a history of unquestionable HAPE if slow ascent is not possible [26]. 60 mg daily of a slow-release formulation should be given, starting with the ascent and ending on the third or fourth day after arrival at the final altitude, if the stay is to be prolonged, or after returning to an altitude below 3000 m or one to which the individual is acclimatised. It should be emphasised that nifedipine helps to avoid HAPE but is not effective for prevention of acute mountain sickness [80]. Interestingly, acetazolamide, which is often used for AMS prevention, blunts hypoxic vasoconstriction in animals [78, 81]. Whether it does so in humans, however, has not been tested and hence it cannot be recommended for this purpose.

Given the uncertainties mentioned above with regard to the preventive effect of inhaled beta-2-receptor agonists, we do not recommend using such drugs instead of nifedipine for the prevention of HAPE. Whether it makes sense to use such drugs (in the dose recommended for treatment of obstructive pulmonary disease) in addition to nifedipine needs to be investigated.

**Treatment**

Immediate improvement of oxygenation is the treatment of choice. Specific recommendations depend on where HAPE occurs. For the mountaineer in a remote area without medical care, descent has first priority while the tourist with HAPE in a resort in the Rocky Mountains may stay at altitude if arterial oxygen saturation can be maintained above 90% with low-flow oxygen (2–4 l/min) and monitoring by family or friends is guaranteed. Relief of symptoms is achieved within hours and complete clinical recovery usually occurs within 2–3 days. Severe, advanced cases need to be evacuated to low altitude, where they may require prolonged hospitalisation [6], especially if there is coexistent HACE.

In Himalayan mountaineers mortality has
been estimated at approximately 50% if neither descent nor any other form of treatment is possible. If descent is impossible and supplemental oxygen is not available, portable hyperbaric chambers [82] and treatment with nifedipine (20 mg slow-release formulation every 6 h) should be initiated until descent is possible. In mountaineers with HAPE at 4559 m, persistent relief of symptoms and improvement of gas exchange and radiographic appearance were documented over 34 h with 20 mg nifedipine every 6 h [29]. There were no significant side effects with nifedipine in this therapeutic trial or when administered as prophylaxis. The question whether inhalation of beta-2-receptor agonists might be used in addition to nifedipine requires investigation. It is likely that sildenafil, which attenuates hypoxic pulmonary vasoconstriction [83] is effective for the prevention and treatment of HAPE, but no clinical trials have yet been reported.

References

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