Seminar

High-altitude illness

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High-altitude illness is the collective term for acute mountain sickness (AMS), high-altitude cerebral oedema (HACE), and high-altitude pulmonary oedema (HAPE). The pathophysiology of these syndromes is not completely understood, although studies have substantially contributed to the current understanding of several areas. These areas include the role and potential mechanisms of brain swelling in AMS and HACE, mechanisms accounting for exaggerated pulmonary hypertension in HAPE, and the role of inflammation and alveolar-fluid clearance in HAPE. Only limited information is available about the genetic basis of high-altitude illness, and no clear associations between gene polymorphisms and susceptibility have been discovered. Gradual ascent will always be the best strategy for preventing high-altitude illness, although chemoprophylaxis may be useful in some situations. Despite investigation of other agents, acetazolamide remains the preferred drug for preventing AMS. The next few years are likely to see many advances in the understanding of the causes and management of high-altitude illness.

In May, 2003, fell the anniversaries of two important high-altitude achievements. May 29 was the 50th anniversary of the first ascent of Mount Everest by Edmund Hillary and Tenzing Norgay. May 8 was the 25th anniversary of the first ascent of Mount Everest without the use of supplementary oxygen by Reinhold Messner and Peter Habeler. Both achievements were once thought to be beyond human capabilities. The fact that these targets were achieved, and have been repeated many times since, is a testimony to the ability of human beings, with the right preparation, to tolerate hypoxia.

Human beings go to high altitudes for many reasons. Around 140 million people live permanently at altitudes higher than 2500 m.[1] Some, such as miners in South America, commute to altitudes up to 6000 m for work. Large numbers of people travel to high altitudes for recreational pursuits, such as mountaineering, trekking, and skiing. The deployment of military personnel to high-altitude areas in Asia as part of regional conflicts in Kashmir and Afghanistan has also become a focus of attention.

High-altitude illness is the collective term for the syndromes that can affect unacclimatised travellers shortly after ascent to high altitude. The term encompasses the mainly cerebral syndromes of acute mountain sickness (AMS) and high-altitude cerebral oedema (HACE), and the pulmonary syndrome high-altitude pulmonary oedema (HAPE). HACE and HAPE occur much less frequently than AMS, but are potentially fatal.

We provide an update on high-altitude illness, with particular emphasis on the current understanding of pathophysiology, prevention, and treatment.

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Epidemiology

The most important risk factors for the development of high-altitude illness are rate of ascent, altitude reached (especially the sleeping altitude), and individual susceptibility. The rate of AMS among conference delegates to moderate altitudes (1920–2957 m) in Colorado, USA, was 25%.[2] In the Mount Everest region of Nepal, about 50% of trekkers who walk to altitudes higher than 4000 m over 5 or more days develop AMS,[3,4] and 84% of people who fly directly to 3860 m are affected.[5] High-altitude illness is much more likely to occur at altitudes higher than 2500 m than at lower altitudes, but is being increasingly recognised at altitudes between 1500 m and 2500 m.[6] The incidence of HACE and HAPE is much lower than for AMS, with estimates in the range 0·1–4·0%.

Other risk factors for high-altitude illness include a history of high-altitude illness and permanent residence lower than 900 m.[2] Exertion is a risk factor for AMS,[7] but lack of physical fitness is not.[8,9] Children and adults seem to be equally affected,[10] but people older than 50 years may be less susceptible to AMS than younger people.[2,11] Although there is generally thought to be no difference between the sexes in susceptibility to AMS, in some studies rates of illness have been higher among women than among men.[5,12,13] Neck irradiation or surgery[14] and respiratory-tract infection[15,16] are potential risk factors for high-altitude illness that warrant further study. Although an association between AMS and dehydration has been noted,[17] it is unclear whether dehydration is an independent risk factor for AMS. The vulnerability of porters and pilgrims to high-altitude illness has been highlighted.[18,19]

Search strategy and selection criteria

We undertook a computer-aided search of PubMed, and used the key words altitude, acute mountain sickness, high-altitude pulmonary edema, high-altitude pulmonary oedema, high-altitude cerebral edema, high-altitude cerebral oedema, hypoxia, and mountaineering. We also reviewed journal reference lists and abstracts from international scientific meetings, and used our existing knowledge of primary publications in the field. Priority was given to recent reports covering topical issues and reports that, in our understanding, have contributed substantially to the current knowledge about high-altitude illness.

AMS and HACE

Clinical presentation

AMS is characterised by non-specific symptoms and a paucity of physical findings. The main symptoms are headache, anorexia, nausea, vomiting, fatigue, dizziness, and sleep disturbance, but not all need to be present. Headache is deemed the cardinal symptom, but the characteristics are not sufficiently distinctive to differentiate it from other causes of headache.[20] Symptoms of AMS typically appear 6–12 h after arrival at high altitude. Diagnostic signs are absent, and the presence of abnormal neurological or respiratory signs can show progression to or development of HACE or HAPE. The non-specific symptoms and signs of AMS can result in diagnostic confusion with other disorders, such as exhaustion, dehydration, hypothermia, alcohol hangover, and migraine.[21]

HACE is widely viewed as the end stage of AMS, and is normally preceded by symptoms of AMS. HACE is characterised by ataxia and altered consciousness, which may progress to coma and death due to brain herniation. People with concomitant HAPE may progress very rapidly from AMS to HACE. Clinical examination may reveal papilloedema, ataxia, retinal haemorrhages, and, occasionally, focal neurological deficits.

Pathophysiology

The pathophysiology of AMS and HACE has been the subject of several reviews.[22–25] The exact mechanism causing these syndromes is unknown, although evidence points to a process in the central nervous system. Characteristics of established AMS include relative hypoventilation,[26] impaired gas exchange,[27] increased sympathetic activity,[28] fluid retention and redistribution,[29] and, in moderate to severe AMS, raised intracranial pressure.[30–32]

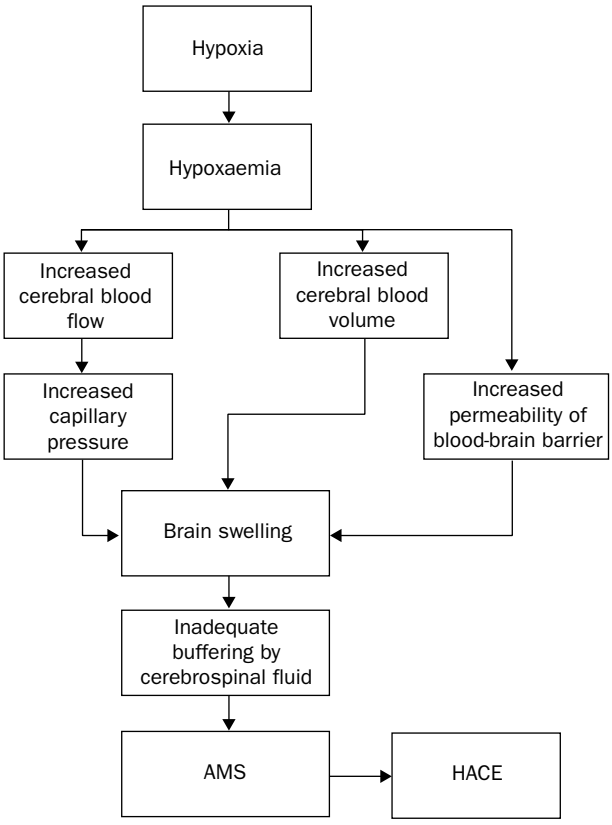

Figure 1: **Proposed pathophysiology of AMS and HACE**

Hackett and Roach[22–24] have proposed a model to explain the pathophysiology of AMS and HACE (figure 1). In this model, hypoxaemia elicits various neurohumoral and haemodynamic responses that ultimately lead to raised cerebral blood flow, altered permeability of the blood-brain barrier, and cerebral oedema. These changes result in brain swelling and raised intracranial pressure. According to the model, AMS occurs in people who have inadequate cerebrospinal capacity to buffer the brain swelling; those with a greater ratio of cranial cerebrospinal fluid to brain volume are better able to compensate for swelling through displacement of cerebrospinal fluid, and are less likely to develop AMS than people with a lower ratio. This hypothesis is attractive, but remains speculative.

Mechanisms that cause brain swelling at high altitude

Fluid accumulation in the brain may be caused by cytotoxic oedema (cell swelling due to increased intracellular osmolarity), vasogenic oedema (leak of the blood-brain barrier with extravasation of proteins and fluid into the interstitial space), or both. Cytotoxic oedema may occur in the later stages of HACE because of increased cerebrospinal-fluid pressure, decreased perfusion, and focal ischaemia, but it does not explain AMS or early HACE. It is unlikely that AMS is associated with hypoxaemia sufficient enough to impair cell-ion homoeostasis and cause cell swelling. By contrast, HACE may be associated with vasogenic oedema. MRI findings among patients with HACE show changes consistent with vasogenic oedema.[33] Further support for the presence of vasogenic oedema include the time course of onset and resolution of symptoms and signs, findings from AMS and HACE in sheep,[34] and the response to corticosteroids (only vasogenic oedema is steroid responsive[35]).

Vasogenic oedema at high altitude probably occurs as a consequence of a combination of factors, each of which cannot on its own explain the process. These factors may include raised cerebral capillary pressure resulting in a mechanical vascular leak,[36] impaired cerebral autoregulation in the presence of hypoxic cerebral vasodilatation,[37] and alteration in permeability of the blood-brain barrier because of hypoxia-induced chemical mediators such as bradykinin, histamine, nitric oxide, arachidonic acid, and vascular endothelial growth factor.[38,39] The angiogenic cytokine, vascular endothelial growth factor, has received particular attention. Gene expression and production of vascular endothelial growth factor, a potent promoter of capillary leakage, is up-regulated by hypoxia and may play a part in the development of AMS and HACE.[39,40] Vascular endothelial growth factor caused hypoxia-induced increase of vascular leakage in the brains of mice.[41] However, preliminary studies of plasma vascular endothelial growth factor concentrations in climbers have been inconsistent and show no association with high-altitude illness.[42,43] Indirect evidence of a role for vascular endothelial growth factor in high-altitude illness comes from the observation that dexamethasone, used in the prevention and treatment of AMS, blocks hypoxic up-regulation of this cytokine.[44]

Mild cerebral oedema as a cause of AMS

Little objective evidence supports the presence of cerebral oedema in AMS. Cerebral oedema was present in a sheep model of AMS and HACE among animals that had the equivalent of moderate to severe AMS.[34] In neuroimaging studies, cerebral oedema has been noted in a few individuals with moderate to severe AMS,[32,45] but it is

unclear whether these people also had HACE. In MRI studies, reduced cerebrospinal-fluid volume,[46] increased T2-weighted signal in the corpus callosum,[47] and increased brain volume[48,49] occurred with ascent to high altitude. These changes suggest the presence of brain swelling, but it is unclear whether this effect is due to cerebral oedema. Furthermore, these changes were not limited to people who had AMS, and provide evidence that all people have some degree of brain swelling on ascent to high altitude. Reports of space-occupying lesions first becoming symptomatic at high altitude[50,51] support the concept of brain swelling at high altitude.

High-altitude headache

Headache is the most common and most prominent symptom of AMS, although its cause remains unclear. Sanchez del Rio and Moskowitz[52] proposed that the cause of high-altitude headache is multifactoral, with various chemical and mechanical factors activating a final common pain pathway, the trigeminovascular system. Triggering factors associated with high-altitude hypoxia may include nitric oxide, arachidonic-acid metabolites, serotonin, and histamine, which sensitise small unmyelinated fibres conveying pain and accumulate in proximity to trigeminovascular fibres, thereby causing headache. The response to non-steroidal anti-inflammatory drugs and steroids provides indirect evidence for involvement of the arachidonic-acid pathway and inflammation in the genesis of high-altitude headache.[53–55] Although high-altitude headache, and AMS in general, share many characteristics with migraine, it is unknown whether similar pathogenic mechanisms are involved in the two disorders. Of note, responses of high-altitude headache to the 5-hydroxytryptamine agonist sumatriptan have been inconsistent.[56–58]

Individual susceptibility

Some people are more susceptible to AMS than others. This fact has prompted substantial efforts by researchers to explain differences in susceptibility and to develop methods for predicting the risk. The role of the hypoxic ventilatory response has been a particular area of interest; the hypothesis is that people who are susceptible to AMS have a decreased ventilatory response to hypoxia. Collectively, the results from high-altitude and hypobaric-chamber studies show a weak association between hypoxic ventilatory response and AMS, with the hypoxic ventilatory response of AMS-susceptible individuals at low altitude being slightly lower than those not susceptible to AMS.[26,59–62] Ventilatory response to carbon dioxide[63,64] and the presence of nocturnal periodic breathing[65,66] do not seem to be associated with susceptibility to AMS.

Ross[67] suggested that susceptibility to AMS may be explained by anatomical differences in intracranial and intraspinal cerebrospinal-fluid capacity. People with a smaller ratio of cranial cerebrospinal fluid to brain volume are less able to tolerate brain swelling through displacement of cerebrospinal fluid than people with higher ratios. These people consequently become more symptomatic from mild brain swelling and are more likely to develop AMS. Preliminary data from neuroimaging measurements support the hypothesis that a tight brain is associated with severity of AMS.[22,23,49] If this hypothesis is correct, elderly people should be less susceptible to AMS than younger adults because of the decrease in brain size that occurs with increasing age. Likewise, infants may have low susceptibility to AMS because of their ability to accommodate brain swelling due to immature cranial sutures and open fontanelles.

Prevention and treatment

Gradual ascent, allowing time for acclimatisation, is the best strategy for preventing high-altitude illness. Determining an ideal ascent rate, however, is difficult, and varies from person to person. One rule of thumb is that at higher than 3000 m, each night should average not more than 300 m above the previous, with a rest day every 2–3 days (or every 1000 m).[68] For many people this ascent rate is too slow, and recommendations now take ascent speed into account and state that the height difference between consecutive sleeping sites should average not more than 600 m per day.[69] Each formula emphasises sleeping altitudes, which means that it is permissible to ascend more than the recommended daily rate, as long as descent is made before sleeping (climb high, sleep low). A night spent at an intermediate altitude (1500–2500 m) before ascent to high altitude will also aid acclimatisation. For example, skiers who are resident at sea level will benefit from a night spent in Denver (1625 m) before a ski vacation in Aspen (base altitude 2400 m). Travellers should be familiar with the symptoms of high-altitude illness and be encouraged not to ascend further if they have these symptoms. It is also helpful to have a flexible travel itinerary so that additional rest days can be incorporated if required.

In some situations, pharmacological prophylaxis may be warranted. These situations include rapid ascent to altitudes higher than 3000 m (eg, flying to La Paz, Bolivia, at 3625 m), and for people with increased susceptibility to AMS. Acetazolamide is the preferred drug, although the ideal dose is undecided. The standard recommendation is 250 mg twice daily, from 1 day before ascent; the drug is widely administered at 125 mg twice daily, but only limited data support the efficacy of this dose regimen.[70] In one systematic review, acetazolamide was judged ineffective as a prophylactic at daily doses lower than 750 mg.[71] This claim runs contrary to clinical experience, and probably reflects the strict criteria for inclusion of studies in the review, and the fact that studies with different ascent rates were compared. Trials directly comparing different doses of acetazolamide in people at similar rates of ascent are needed to clarify this issue. Dexamethasone is also effective for AMS prophylaxis (normal dose 8 mg daily in divided doses),[72–74] and is frequently the alternative if acetazolamide cannot be prescribed. Acetazolamide is probably slightly more effective than dexamethasone,[75] and the combination of both drugs is more effective than either alone.[76]

Preliminary evidence shows that *Gingko biloba* has some prophylactic activity against AMS. During an ascent from 1800 m to 5200 m over 10 days, no person taking gingko extract at a dose of 80 mg twice daily experienced AMS, compared with 41% of people taking placebo.[77] Gingko 120 mg twice daily taken for 5 days before exposure reduced the incidence and severity of AMS during ascent from 1400 m to 4300 m over 2 h.[78] In a third study, gingko 60 mg three times daily, started 1 day before rapid ascent from sea level to 4205 m, compared with placebo, reduced the severity but not rate of AMS.[79] By contrast, gingko was no better than placebo in preventing AMS in trekkers ascending from 4248 m (BB, unpublished data). Gingko's effects may be due to its antioxidant activity. This concept is supported by data suggesting that ingestion of antioxidant vitamins may reduce the incidence and severity of AMS.[80]

The principles of treatment for AMS are to avoid further ascent until symptoms have resolved, to descend if there is no improvement or if symptoms worsen, and to descend immediately at the first signs of cerebral or

pulmonary oedema. Rest alone is frequently sufficient for mild AMS; analgesics and antiemetics may afford symptomatic relief. Descent and oxygen are the treatments of choice for moderate to severe AMS. Even a small descent of 400–500 m may be sufficient to relieve symptoms. Additional pharmacotherapy may be used in conjunction with the treatments already mentioned, especially if descent is impossible and oxygen is unavailable. Acetazolamide 250 mg twice or three times daily and dexamethasone 4 mg every 6 h to help lessen the severity of symptoms of AMS.[45,53,72,81] Simulated descent in a portable hyperbaric chamber is also effective,[82–84] and may be particularly useful when descent is impossible. The treatment for HACE is immediate descent in conjunction with oxygen, if available, and dexamethasone.

HAPE

Clinical presentation

HAPE typically occurs in the first 2–4 days after arrival at altitudes higher than 2500 m, and is not necessarily preceded by AMS. Risk factors for HAPE are the same as for AMS and HACE. In addition, HAPE may be over-represented in men compared with women, and cold is a risk factor.[85] People with abnormalities of the cardiopulmonary circulation that are associated with increased pulmonary blood-flow pressure, such as unilateral absence of a pulmonary artery or primary pulmonary hypertension, or both, are at increased risk of HAPE, even at moderate altitudes.[86,87]

The first symptoms of HAPE are generally dyspnoea on exertion and reduced exercise tolerance greater than expected for the altitude. Cough, dry and annoying at first, becomes productive later in the illness with blood-stained sputum. Physical findings may be initially subtle. Tachypnoea and tachycardia are present at rest as the illness progresses, and fever is common, although rarely exceeding 38·3°C. Crackles are evident on chest auscultation. HAPE is frequently accompanied by signs of HACE. There is no radiographic feature specific to HAPE,[88] and electrocardiography may show evidence of right-ventricular strain.

The existence of a subclinical form of HAPE was addressed by Cremona and colleagues.[89] Among a group of climbers on Monte Rosa (4559 m), 77% had indirect evidence of pulmonary extravascular fluid accumulation based on increased closing volumes. Exercise at sea level is also associated with increased pulmonary artery pressure and transvascular fluid flux, and the contributions of exercise and hypoxia to the findings from this study are uncertain. If these findings are related to subclinical pulmonary oedema, it is also unclear whether this is a prognostic factor for the development of clinically relevant HAPE.

Pathophysiology

HAPE is a non-cardiogenic pulmonary oedema characterised by exaggerated pulmonary hypertension leading to vascular leakage through overperfusion, stress failure, or both. The exact mechanism that causes the accentuated hypoxic pulmonary vasoconstriction is unclear. Undoubtedly, several factors combine to render an individual susceptible to HAPE (figure 2).

Mechanisms accounting for exaggerated pulmonary hypertension

Pulmonary artery pressures and pulmonary vascular resistance are high in HAPE, but HAPE is not due to left-ventricular failure. Furthermore, individuals susceptible

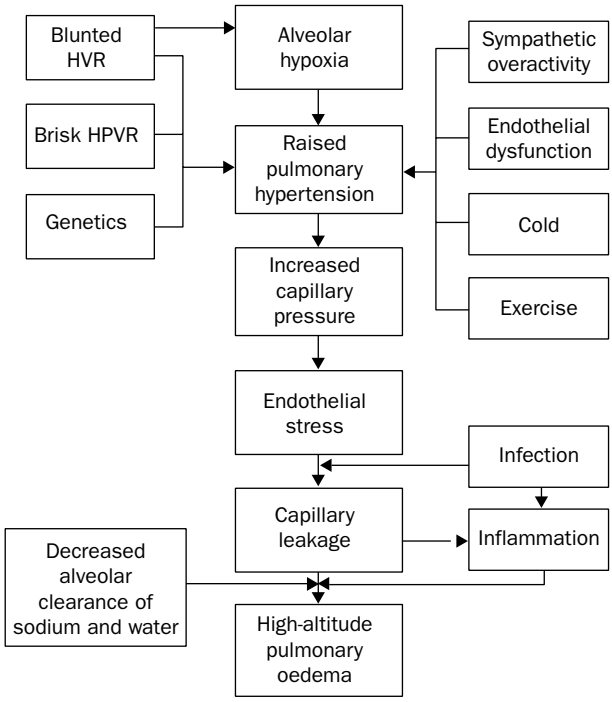

Figure 2: **Proposed pathophysiology of high-altitude pulmonary oedema**

HVR=hypoxic ventilatory response. HPVR=hypoxic pulmonary vascular response. Based on reference 108.

to HAPE have an exaggerated rise in pulmonary artery pressure in response to hypoxia[90] and exercise,[91] and drugs that lower pulmonary artery pressure are effective for the treatment and prevention of HAPE.[92–96] Evidence shows that the abnormal rise in pulmonary artery pressure is accompanied by an increase in capillary pressure at the onset of HAPE, with a threshold of 19 mm Hg for the development of clinical HAPE.[97]

There are several possible causes of the pulmonary hypertension seen in HAPE. Hultgren[98] proposed that uneven hypoxic pulmonary vasoconstriction may cause regional overperfusion of capillaries in areas of least arterial vasoconstriction, leading to increased capillary pressure and leakage. Support for this concept is provided by radioisotope perfusion studies,[95] and by the increased susceptibility to HAPE among people with pulmonary circulation abnormalities associated with overperfusion of restricted pulmonary vascular beds.[86,87]

Endothelial dysfunction may also play a part in causing the excessive pulmonary hypertension of HAPE through impaired release of relaxing factors and augmented release of vasoconstrictors. Inhalation of nitric oxide, an endothelium-derived relaxing factor, decreases systolic pulmonary artery pressure in people susceptible to HAPE to the level of people not susceptible to HAPE.[95] Furthermore, exaggerated hypoxic pulmonary vaso-constriction is associated with impaired nitric-oxide synthesis.[99–101] These findings and those from genetic studies[102] support the hypothesis that HAPE-susceptible people may have a defect in nitric-oxide synthesis, possibly due to reduced nitric-oxide synthase activity. The endothelium also synthesises vasoconstrictor factors. Endothelin-1 is one such factor thought to play an important part in regulation of pulmonary vascular tone.[103] At high altitude, endothelin-1 concentrations are higher in mountaineers prone to HAPE than those resistant to HAPE.[104] Moreover, there is a direct relation between altitude-induced increase in plasma

endothelin-1 concentration and systolic pulmonary artery pressure, as well as the endothelin-1 plasma concentration and the pulmonary artery pressure measured at high altitude.

People susceptible to HAPE exhibit exaggerated sympathetic activation during short-term hypoxic breathing at low altitude and during high-altitude exposure.[105] These findings led to speculation that increased sympathetic activity may contribute to the exaggerated pulmonary hypertension in HAPE. Consistent with this concept, in HAPE, α-adrenergic blockade leads to improved haemodynamics and oxygenation compared with other vasodilators.[92]

Exercise and cold lead to increased pulmonary intravascular pressure, and may be contributing factors to the development of HAPE. High-intensity exercise may induce high protein pulmonary oedema in human beings and animals, presumably through stress on the pulmonary vasculature.[106,107] Cold probably increases pulmonary artery pressure through sympathetic stimulation, and has been noted as a risk factor for HAPE in Colorado.[85]

Role of inflammation

Whether the alveolar capillary leak in HAPE is caused by an inflammatory process, much like in acute respiratory distress syndrome, or by high microvascular pressures is unclear. Evidence for the presence of inflammation in people with HAPE has come from several sources. Many patients with HAPE have fever, peripheral leukocytosis and raised erythrocyte sedimentation rates.[108] Examination of bronchoalveolar lavage fluid from two groups of patients with HAPE (climbers on Mount McKinley and patients admitted to hospital in Japan) have shown a striking cellular response, with raised concentrations of proinflammatory mediators and cytokines, that returned to normal after recovery from HAPE.[109–112] Further evidence for an inflammatory component of HAPE is provided by the high rate of preceding respiratory-tract infection in children who develop HAPE,[16] the association between certain major HLA-immunomodulating alleles with susceptibility to HAPE,[113] and raised plasma E-selectin concentrations in hypoxaemic climbers with AMS and HAPE.[114]

One study has provided evidence that inflammation is not a primary event in the pathogenesis of HAPE. Swenson and colleagues[101] collected bronchoalveolar fluid from a small group of climbers at 4559 m in the Swiss Alps. Analysis of this fluid showed no rise in neutrophils or inflammatory mediators. The differences between the Mount McKinley and Japanese studies might be explained by the timing of the lavages. In the earlier studies bronchoalveolar lavage was done after HAPE was well established, generally 1–2 days after onset. Swenson and colleagues did bronchoscopy very early in the course of illness, mostly within 3–5 h. They reason that the inflammation associated with HAPE is a secondary event that occurs as a consequence of alveolar flooding. Support for this argument comes from prospective studies measuring inflammatory markers (including plasma cytokines, urinary leukotriene E_4 excretion, and markers of in-vivo thrombin and fibrin formation) showing no evidence of inflammation before or at the onset of HAPE.[115–117]

Although inflammation may not be a primary event in HAPE-susceptible individuals, people who are constitutionally resistant to HAPE may develop the disorder if factors favouring increased permeability, such as inflammation, are present. Such a situation may arise after a viral lower-respiratory-tract infection.

Alveolar-fluid clearance

The alveolar epithelium has an important role in the fluid balance of the lung. Sodium is taken up by the alveolar cells at the apical surface and is transported out of the cell across the basolateral membrane by sodium, potassium ATPase.[118] Blunting of this process may impair clearance of alveolar fluid and predispose individuals to pulmonary oedema.

In one study, impaired alveolar fluid clearance was thought to have a role in the development of HAPE. In a double-blind, randomised, placebo-controlled study of HAPE-susceptible mountaineers, prophylactic inhalation of the β-adrenergic agonist salmeterol reduced the incidence of HAPE by 50%.[119] β-adrenergic agonists up-regulate the clearance of alveolar fluid and lessen pulmonary oedema in animal models,[120,121] although salmeterol may have additional haemodynamic actions that also help prevent HAPE. In the same study, at low altitude, the nasal transepithelial potential difference, a marker of transepithelial sodium and water transport in the distal airways, was more than 30% lower in HAPE-susceptible people than in non-susceptible people. These findings suggest that sodium-dependent absorption of fluid from the airways may be defective in people susceptible to HAPE, and support the concept that alveolar fluid clearance may have a pathogenic role in pulmonary oedema.

Characteristics of extravasation in HAPE

Stress failure of pulmonary capillaries due to high microvascular pressure has been postulated as the final process in HAPE that leads to extravasation of blood cells and plasma.[122,123] Disruption of alveolar epithelium and endothelium have been noted in the lungs of rabbits perfused under high pressure[124] and in rats exposed to high altitude.[122] This concept would account for the mild alveolar haemorrhage seen among patients with HAPE,[101] but whether this mechanism entirely accounts for the high permeability leak in HAPE is unclear. The lack of increased bronchoalveolar-lavage fluid leukotriene B_4[125] and lack of activated intravascular coagulation[116] due to exposure of basement membranes in early HAPE mitigate against early capillary stress failure. The leak might initially be due to a non-traumatic alteration in the normal selectivity of the alveolar-capillary barrier to high-molecular-weight molecules, and that capillary stress failure is a late phenomenon. The possibility that the leak is sited more proximally in the pulmonary vasculature has not been discounted.[126]

Role of genetic factors

Gene polymorphisms that confer differences in the activities of key enzymes may play a part in the pathogenesis of HAPE. At present, only limited data are available. Endothelial nitric-oxide-synthase gene polymorphisms were associated with susceptibility to HAPE in Japan,[102] but not in Europe.[127] Although angiotensin-converting-enzyme gene polymorphism may confer a performance advantage at high altitude,[128] there is no clear association with susceptibility to HAPE.[129] Susceptibility to HAPE and susceptibility to primary pulmonary hypertension share some physiological similarities, but preliminary data suggest that the two disorders have different genetic backgrounds.[130]

Prevention and treatment

As for AMS and HACE, the best way to prevent HAPE is to ascend gradually to allow sufficient time for acclimatisation. In people with a history of HAPE, 20 mg

slow-release nifedipine every 8 h prevented HAPE after rapid ascent to 4559 m.[94] Inhaled β-adrenergic agonists may also be useful in the prevention of HAPE.[119]

Early recognition is the first key step in the treatment of HAPE. Thereafter, descent and supplementary oxygen are the most effective therapies. Exertion should be kept to a minimum. If oxygen is unavailable and descent is impossible, treatment in a portable hyperbaric chamber may be life-saving, although the recumbent position necessary for operation may not be tolerated by the patient. Continuous positive airway pressure may also be useful for the treatment of HAPE; a portable device has been developed that can be used in the mountains.[131] 10 mg nifedipine, followed by 20–30 mg slow release every 12–24 h may be useful as an adjunct to descent and oxygen.[93]

Future directions

Although the epidemiology of high-altitude illness has been extensively investigated, there are several unresolved issues. What are the precise roles of age, sex, exercise, and respiratory-tract infection in susceptibility to AMS and HAPE? Research should continue to search for the genetic basis of high-altitude illness. These efforts will aid the understanding of the pathophysiology of AMS, HACE, and HAPE, and may provide markers of susceptibility to high-altitude illness.

Studies investigating the pathophysiology of high-altitude illness should focus on the time period immediately after exposure to high altitude to observe the complete time sequence of changes that occur in response to hypobaric hypoxia. High-resolution scanning such as MRI, positron emission tomography, and single-photon CT techniques will allow investigators to characterise changes in the lungs in HAPE (eg, inhomogeneous hypoxic vasoconstriction) and in the brain in AMS and HACE (eg, quantification of blood-brain-barrier leakage and of the ratio of brain volume to intracranial volume). An animal model of HAPE will help resolve many issues, including the sequence of events that lead to a permeability leak, the time course for the appearance of inflammatory markers, the role of sodium and water reabsorption, and the efficacy of various agents for prophylaxis and treatment. Experiments with selective stimulants of alveolar sodium transport will help clarify the role of this process in the development of HAPE. For AMS and HACE, better characterisation of the substances that alter permeability of the blood-brain barrier is needed, and may identify new potential therapeutic targets.

We need to improve our ability to advise travellers about their individual risk of AMS and ideal ascent rates to prevent this disorder. Research may involve the identification of markers of susceptibility and incorporation of these markers into mathematical models to predict the likelihood that AMS will develop.[132] This goal can be achieved only by establishing comprehensive databases of individual ascent profiles linked to demographic data and measurements of AMS, similar to Project Dive Exploration for underwater diving.[133] Drugs with activities that may help prevent or treat high-altitude illness, such as gingko, sildenafil,[134] and garlic,[135] need further assessment.

Conflict of interest statement
None declared.

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