

Altitude Related Disorders and Their Management

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Abstract: Altitude related medical problems cause significant avoidable morbidity and mortality. Acute mountain sickness, high altitude pulmonary and cerebral edema are potentially serious disorders. Many high altitude places are remotely located and away from medical help. It is imperative for persons travelling to such places to be able to recognize symptoms of common problems and manage them accordingly. The potentially serious consequences of these diseases and poor effectiveness of treatment modalities underscore the need for prevention. The preventive measure are screening to identify subjects at risk and providing information to mountaineers. This review aims to highlight common altitude related illnesses, their aetiologies and current management. The effect of high altitude in special high risk population is also discussed in this review.

Introduction

Mountains have fascinated and attracted mankind for millennia. Most peaks in the Alps had been climbed by the end of the 19th century. Some early climbers mentioned experiencing the symptoms now described as mountain sickness. By the beginning of the 20th century, hypoxia was known to be the main cause of these symptoms. Even today, many questions regarding the precise mechanism of altitude illness remain unanswered.

A multitude of problems is associated with ascent to altitude. Some of these are merely an annoyance while others are life threatening. Fundamentally, all are caused by a lack of oxygen. However, in most cases, considerable uncertainty exists regarding to the precise pathophysiology of these illnesses. Three major *syndromes*, acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE), are now commonly accepted. Other related problems, such as impaired sleep at high altitude, often coexist with the major syndromes and also deserve mention. Finally, the effects of ascent on certain special populations are discussed in this article.

Acute Mountain Sickness

Acute mountain sickness (AMS) is a condition affecting lowlanders 6-90hrs after rapid ascent to altitude. It is characterized by lethargy, insomnia, headache, nausea, vomiting and dyspnoea. In severe forms cyanosis, crepitation in the lungs, papilledema and other signs of cerebral edema are also features. A consensus conference was held during the 1991 Hypoxia and Mountain Medicine Symposium at Lake Louise, Canada to define the various altitude syndromes¹. This group defined AMS as follows: "In the setting of a recent gain in altitude, the presence of headache and at least one of the following symptoms: gastrointestinal (anorexia, nausea or vomiting), fatigue or weakness, dizziness or lightheadedness, difficulty in sleeping." AMS is defined by its symptoms, but the exact cause of AMS is still unknown; cerebral edema may play a role.

Many factors affect the incidence and severity of AMS, such as the rate of ascent, altitude attained (especially altitude of sleep), duration of exposure to altitude, and amount of exercise undertaken at altitude. The most important and least understood variable is the underlying physiological susceptibility of the individual. Few people experience significant symptoms below 7000-8000 ft (2130-2440m), whereas portable hyperbaric bags (eg, Gamow bag) simulate descent to a lower altitude. These bags are effective for treating AMS, although they are rarely needed unless AMS is

complicated with high-altitude cerebral or pulmonary edema.

The exact mechanism by which hypoxia causes AMS is still unknown, although hypoventilation probably is important. The role of fluid retention as a cause of AMS remains uncertain. Antidiuretic hormone and atrial natriuretic secretion factor are altered in AMS, suggesting that CNS changes that cause secretion of hormones promoting fluid retention may be important⁷. Sutton and Lassen⁸ suggested that hypoxia stimulates increased cerebral blood flow, resulting in vasogenic cerebral edema. Multiple factors lead to the development of AMS, but the exact role each of these plays in the development of this disorder is unknown.

Sleep at High Altitude : Most newcomers to altitude frequently report difficulty in sleeping at night, even in the absence of other symptoms. Sleep disruption at altitude results from a combination of many factors, including the cold windy environment and the often-crowded sleeping conditions, in addition to hypoxia periodic breathing during sleep causes further disruption of sleep continuity. At extreme altitude, loss of sleep is nearly complete, further compromising the energy of already exhausted climbers.

Frequent nighttime awakenings and arousals represent the major disruptors of high-altitude sleep. The Operation Everest II (OEII) decompression chamber study provided an opportunity to monitor changes in sleep across various altitudes up to an altitude equivalent to the South Col of Mount Everest (approximately 8040m, barometric pressure 282 mm Hg). These studies found severe sleep fragmentation and periodic breathing (with central sleep apneas) at all altitudes studied but especially at the highest altitudes. These brief 2- to 5-second arousals from sleep (not full awakenings) increased from an average of 22 + 6 times per hour at sea level to 161 + 66 times per hour at 25,000 ft (7620m, 282mm Hg)⁹.

Periodic breathing is a common breathing pattern during sleep at high altitude. Changes in sleep site, as well as conflicting effects of hypocapnia and hypoxia on the peripheral chemoreceptors, lead to a most unacclimatized person ascending to 10,000 ft (3050 m) or higher experience at least a few symptom².

Treatment and Prevention of AMS : Slow, gradual ascent with adequate time for acclimatization provides the best protection from AMS. The ideal ascent rate varies based on individual susceptibility to AMS. Once symptoms of AMS occur, additional time for acclimatization before ascending further usually is the only treatment needed for mild AMS. If symptoms worsen despite additional time for acclimatization, descent to a lower altitude (especially sleeping altitude) is needed. A descent of 1000-3000 ft (300-900m) usually is sufficient to ameliorate symptoms. Supplemental oxygen, although rarely available in sufficient quantities, also effectively relieves symptoms of AMS³.

Pharmacological Treatment of AMS : Acetazolamide (Diamox)

is effective both for the prevention and for the treatment of AMS. Forward et al⁴ (1968) demonstrated that 250mg of acetazolamide every 8 hours dramatically reduced symptoms of AMS compared to people taking a placebo during a stay at the 12,800-ft (3900-m) summit of Mount Evans, Colorado. Others have confirmed these findings, and Sutton et al⁵ found that acetazolamide decreased hypoxemia during sleep by reducing the amount of periodic breathing. The mechanism of action of acetazolamide in AMS is unclear. The drug is a carbonic anhydrase inhibitor that causes a bicarbonate diuresis, resulting in metabolic acidosis. It also decreases production of cerebrospinal fluid. However, these actions do not adequately explain the effectiveness of acetazolamide in AMS. Current recommendations are 125-250 mg twice daily starting one day before ascent and continuing for a couple of days at altitude or even for the duration of stay at altitude. Smaller doses may be effective in some people.

Dexamethasone, 2-4 mg every 6 hours, is also effective in preventing and treating AMS. The mechanisms of action of dexamethasone in relieving AMS symptoms are unknown. Its relative effectiveness compared to acetazolamide has not been established, but it likely is equivalent to acetazolamide⁶ destabilization of the respiratory control system, which is responsible for the periodic breathing observed at high altitude¹⁰. Much of the sleep disruption at high altitude has been attributed to periodic breathing. Transient arousals from sleep commonly occur at the onset of the hyperpneic phase of periodic breathing. Nearly one half of the apneic episodes observed in the OEII study were not associated with electroencephalogram (EEG) arousals. Thus, a complex interplay exists among sleep state ventilatory responsiveness, breathing pattern, and sleep fragmenting arousals⁹.

Nighttime arterial oxygen saturation is lower than daytime (awake) values and thus represents the most profound hypoxic insult during a high-altitude sojourn. The mean arterial oxygen saturation (SaO₂) at night during the OEII studies at 25,000 ft (7620m) was only 52±2% compared with a daytime SaO₂ of 71±7%. The lower nighttime SaO₂ may, in part, result from periodic breathing, although others have suggested that periodic breathing actually improves nighttime SaO₂. Periodic breathing appears to be a risk factor for high altitude illness, and carbonic anhydrase inhibitors (eg, acetazolamide) decrease nocturnal periodic breathing, improve arterial oxygen saturation, and ameliorate daytime symptoms of AMS¹¹.

High-Altitude Pulmonary Edema (HAPE)

High altitude pulmonary edema (HAPE) is a serious and potentially life-threatening manifestation of altitude illness. The first symptoms of HAPE occur 1-3 days after arrival at altitude. In adults, these symptoms commonly occur after exercise and consist of cough, shortness of breath, chest tightness, and fatigue. In approximately half the cases, these symptoms are associated with the typical symptoms of AMS. Initially, cough is nonproductive, but thin, clear, or yellowish sputum is later produced. In some cases, the sputum is tinged with blood. Fatigue may be the first symptom, occurring even before dyspnea develops and manifesting as the inability of the affected individual to maintain the pace of the group. Physical findings in HAPE include cyanosis, temperature as high as 101°F (38.5°C, a higher fever creates suspicion of pneumonia), flat neck veins, and crackles over the mid chest. Heart and respiratory rates are increased. The incidence of HAPE is affected by factors such as rate of ascent, age, sex, physical exertion, and, most importantly, individual susceptibility¹².

A form of HAPE known as reascent HAPE or reentry HAPE occurs in acclimatized individuals who descend to lower altitude and then reascend. In these cases, individuals usually spent 3-5 days or as many as 10-14 days at low altitude before returning to higher elevations. For unknown reasons, these individuals have

an increased likelihood of developing HAPE.

Diagnosis : The diagnostic criteria for HAPE are at least 2 symptoms and 2 signs from the following list, in the setting of a recent gain in altitude :

* *Symptoms* (at least 2) - Dyspnea at rest; - Cough; -Weakness, decreased exercise performance; - Chest tightness or congestion

* *Signs* (at least 2) - Rales or wheezing in at least one lung field; - central cyanosis; - tachypnea; - tachycardia.

A chest radiograph, if facilities are available, and a measurement of arterial oxygen saturation may contribute to making the diagnosis and excluding other disorders. Marked hypoxemia is an important and common finding in HAPE.

Radiographic features : With HAPE, homogeneous or patchy opacities appear in the mid lung areas and involve one or both sides of the chest. Opacities are more likely to be present in the right lung than in the left lung. Unilateral involvement of only the left lung is rare and should raise the suspicion of a congenital absence or hypoplasia of the right pulmonary artery. The pulmonary arteries frequently are enlarged; however, the cardiac silhouette usually is normal. Kerley lines may or may not be present.

Pathophysiology : A clear understanding of the precise etiology of HAPE and the mechanism for its development is hampered by the lack of a good animal model. Any hypothesis must account for several factors, as follows : (1) elevated pulmonary artery pressures with wedge and left atrial pressures within the reference range, (2) no evidence of left ventricular failure, (3) capillary and arterial thromboses (in many fatal cases of HAPE), and (4) intense exercise (makes HAPE more likely, while bedrest is beneficial).

Hypoxic pulmonary vasoconstriction occurs, to some extent, in everyone who ascends to high altitude, however, the level of vasoconstriction is highly variable. Individuals with HAPE have more severe pulmonary hypertension than is usual at altitude, but not everyone with pulmonary hypertension of similar severity develops HAPE.

Hultgren¹² proposed the *overperfusion concept* as the mechanism for developing HAPE. This overperfusion mechanism postulates that uneven pulmonary vasoconstriction results in lung areas with decreased blood flow while other areas receive excessive flow. These overperfused lung areas are where the proposed leakage of edema fluid occurs. Bronchoalveolar lavage studies show that the edema fluid in HAPE has a high protein concentration, along with various inflammatory markers, such as complement C5a and leukotriene B4. West et al¹³ suggested that HAPE results from a rupture of pulmonary capillaries subjected to high wall stresses from high pressure in the vessels. The nonhomogeneous vasoconstriction proposed by Hultgren would allow high pulmonary artery pressures to be transmitted to pulmonary capillaries in overperfused areas of the lung.

Treatment of HAPE : Both the overperfusion and stress failure models for HAPE imply that a reduction of the excessive hypoxic pulmonary vasoconstriction is critical for the treatment of HAPE. Oxygen and descent to low altitude both result in lowered pulmonary artery pressure. Rapid descent to lower altitude results in dramatic symptomatic improvement. Often, a descent of only 1000-3000 ft (300-900m) is necessary. Thus, descent is the most important therapeutic modality. Early descent, before HAPE becomes severe, potentially can save more lives than any other treatment.

Use of supplemental oxygen reduces pulmonary artery pressure; however, sufficient quantities of oxygen are rarely available under field conditions, precluding reliance on oxygen alone. Nifedipine and other vasodilators also are useful in treating HAPE. Patients with HAPE who were treated by Oelz et al¹⁴ with 10mg nifedipine followed by 20mg of slow-release nifedipine every 6 hours showed

improvement in oxygenation and overall condition, even without descent to lower altitude. Oter vasodilators may also decrease pulmonary artery pressure and be useful in treating HAPE. Reliance on these medications should not delay early and rapid descent.

Portable hyperbaric bags (eg, Gamow bag) are now available. These fabric hyperbaric chambers increase the pressure approximately 2 pounds per square inch (PSI), ie 103mm Hg, simulating descent, which is effective in treating HAPE¹⁵.

The best treatment is prevention of HAPE by gradual ascent and early recognition of HAPE symptoms; nifedipine is useful in preventing HAPE among susceptible individuals.

High Altitude Cerebral Edema (HACE)

High altitude cerebral edema (HACE) is an extreme form of mountain sickness. The lake louise definition¹ states that HACE "can be considered 'end stage' or severe AMS. In the setting of a recent gain in altitude, [HACE is] the presence of a change in mental status and/or ataxia in a person with AMS, or the presence of ataxia in a person without AMS." Without prompt treatment, further neurological deterioration and death are likely.

Signs and symptoms of HACE may progress rapidly (within 12h) from minimal manifestations to coma. Typically, this progression occurs slowly. Often the symptoms of HACE begin at night, occasionally resulting in a loss of consciousness during sleep. Most cases of HACE occur after individuals have been at altitude for several days.

The pathophysiology of HACE shares many similarities with the pathophysiology of AMS. Despite similarities, the reason only a few persons with AMS develop HACE is unclear. MRI in patients with HACE shows edema of the white matter, especially in the corpus callosum. Hansen et al¹⁶ suggested that cytotoxic cellular edema of the brain from hypoxia caused many of the signs and symptoms of both AMS and HACE. Lassen¹⁷ however, suggested that HACE was caused by vasogenic edema resulting from increased cerebral blood flow, causing leakage of fluid into the brain. Recently, Severinghaus¹⁸ has proposed roles for angiogenesis, osmotic swelling and ischemia in the pathogenesis of HACE.

Treatment : Mild cases of AMS do not require descent to lower altitude, whereas HACE may be lethal if not recognized and promptly treated; thus, early recognition of HACE is crucial. A change in the level of consciousness or the onset of ataxia requires immediate descent.

Supplemental oxygen, if available, should be administered along with dexamethasone at 4-8 mg initially and then 4mg every 6 hours thereafter. Diuretics, such as furosemide and mannitol, should not be administered because they may result in orthostatic hypotension from decreased intravascular volume, which makes descent difficult or impossible.

Early use of a hyperbaric bag (ie, Gamow bag) may relieve symptoms and make descent easier but should not be considered a substitute for descent, especially because recovery often requires 10 or more days, even with treatment at low altitude.

Special population at High Risk

Large numbers of individuals go to high altitudes for work and recreation, and some individuals have special medical problems. Despite similarities to altitude illness in healthy individuals, ascent to high altitude by person with underlying cardiac disease, pulmonary disease, and sickle cell anemia deserves special mention.

Coronary Artery Disease

Unacclimatized persons with coronary artery disease may develop increased anginal symptoms following ascent to altitude because of an increase in cardiac work, as well as possible vasoconstriction

of the coronary arteries. Cardiac arrhythmia, including atrial fibrillation or flutter, may worsen after rapid ascent to altitude, even without underlying coronary artery disease¹⁹. During exercise testing at 10,150ft (3100 m), cardiac patients developed angina or ST segment depression at the same double product (ie, heart rate times systolic blood pressure) as they did at 5280 ft (1600m). Thus, ascent to altitudes of 10,000 ft (approximately 3000m) has little direct effect on myocardial ischemia but may produce symptoms by increasing heart rate and blood pressure during submaximal exercise²⁰.

Despite the increase in cardiac symptoms following rapid ascent to high altitude, the increased risk for cardiac death is low. Hultgren¹⁹ reviewed the effects of altitude on patients with cardiovascular disease and suggested an approach (including when to perform a pre-ascent exercise test) for the evaluation of a patient with heart disease prior to trekking at high altitude.

Pulmonary Disease

Chronic obstructive pulmonary disease : Shortness of breath occurs in everyone, including those without heart or lung disease, after ascent to altitude. Even at sea level, patients with COPD frequently are limited by impaired lung mechanics and dyspnea.

Because of the increased ventilatory requirements of exercise at altitude, patients with COPD may experience a worsening of their symptoms during exposure to altitude. Patients with COPD without evidence of cor pulmonale were exposed to 6300-ft (1920-m) altitude by Graham and Houston²¹. These patients developed few altitude-related symptoms except fatigue (and headache in one individual), despite a decrease in resting arterial partial pressure of oxygen (PO₂) from 66 to 52mm Hg. In these patients, the authors attributed the lack of symptoms of AMS to partial acclimatization resulting from hypoxemia. They concluded that patients with mild or moderate COPD without cor pulmonale tolerate altitude exposure quite well. Patients with COPD living at altitude, as opposed to sojourners, develop cor pulmonale and have an increased mortality rate when compared to similar patients living at low altitude. Although the cause for this increased mortality rate is unknown, it probably is related to the higher pulmonary artery pressure observed in these residents²².

Pulmonary hypertension : Hypoxic pulmonary vasoconstriction raises pulmonary artery pressure in sojourners to high altitude. With primary pulmonary hypertension, ascent to altitude results in even higher pulmonary artery pressures. These patients are likely to experience additional symptoms, such as fatigue, dyspnea, or even syncope. An increase in supplemental oxygen or the use of pulmonary vasodilators may be helpful to ameliorate altitude symptoms.

Asthma : The dry, cold air often encountered at high altitude may cause bronchoconstriction; however, this climate also contains fewer allergens. As a result, many people with asthma report doign as well ro even better at high altitude than at lower elevations. The reduced barometric pressure results in decreased air density. Thus, even though the ventilatory demands of activity at high altitude are reater, the reduced air density at least partially compensates. Patients with asthma who want to travel to high altitude should be encouraged to do so, but they should bring an adequate supply of their medications and pay attention to their respiratory symptoms.

Sickle Cell Disease

Many genetic variations occur in the hemoglobin molecule. A far more common hemoglobinopathy occurs in individuals with sickle cell disease and makes ascent to high altitude inadvisable. Sickle cell disease refers to several types of abnormal hemoglobins, including hemoglobin AS and hemoglobin S. Under conditions of hypoxia, the red blood cells in these individuals become deformed and take on the shape of a sickle, causing blood viscosity to

increase, cells to clump together more readily, and microcirculation to become blocked. The concentration of hemoglobin S in the circulation is the major determination of sickling. Bone pain and splenic infarction may occur²³.

Most of these individuals have sickle cell trait and are largely asymptomatic, while a few have a far more severe condition, sickle cell anemia. Those with sickle cell anemia probably already know about their disease, but those with only sickle cell trait may be unaware of the problem and, therefore, are more likely to go to high altitude and experience problems.

Exposure to the hypoxia at high altitude may precipitate a sickle cell crisis among those patients with sickle cell anemia. These individuals should not attempt to go to high altitude. Even the modest hypoxemia associated with airline travel may precipitate symptoms in susceptible individuals.

- Consider providing supplemental oxygen to those individuals with sickle cell anemia during aircraft flights. Travel by commercial airline generally is safe for patients with sickle cell trait, however, rarely, they may experience symptoms during airplane flights. Similarly, those with sickle cell trait generally tolerate altitudes of 8000-10,000 (2440-3048m) without difficulty, although a few may become symptomatic.

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