

Smith Seminars
Online Continuing Education
AARC-Approved for 2 CRCE
Altitude-Related Disorders

Objectives

- Be able to describe the various medical problems associated with ascent to high altitude
- Understand the altitude-related symptoms through acclimatization
- Know the treatment of the altitude-related disorders when they occur
- Become familiar with the effects of ascent on certain special populations

Mountains have fascinated and attracted humankind for many generations. 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. Despite the obvious dangers inherent in climbing and the altitude-related illness experienced by nearly all who spend significant time in the mountains, people continue to seek the remoteness and pleasures of high places. With the availability of easy transportation into the mountains, not just for climbing but also for skiing and other forms of recreation, thousands are exposed to high altitude each year. These individuals frequently experience acute illness soon after ascent. With longer stays at altitude, these symptoms improve in a process known as acclimatization. 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 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.

Effects of Altitude

Studies of the effects of chronic hypoxemia can be performed in the laboratory by decreasing either the concentration of inspired oxygen or the barometric pressure in a hypobaric chamber. Nature has provided a third option, high altitude, which allows the examination of the effects of chronic hypoxemia in individuals under varying conditions. Thus, studies of high-altitude physiologists are of interest to not only mountaineers and aviators but also physicians. Knowledge gained on mountain peaks may give insight into the pathophysiology of patients with cyanotic heart disease or chronic lung disease. Finally, physicians caring for patients who already have hypoxemia should understand the alterations provoked by changes in altitude that may affect these patients while they are living in or visiting mountainous regions or traveling by air.

High altitude has generally been defined as above 3000 m, or approximately 10,000 ft. In healthy persons, clinically significant changes are difficult to demonstrate at elevations lower than this. Many people live at high altitude and perform normal activities. Mountaineers and

aviators have experimented with humans' ability to function and survive at extreme altitudes. The 1978 and later conquests of Mount Everest (8884 m [about 29,140 ft]) without supplemental oxygen tested man's ability to survive in a severely hypoxemic environment. At that altitude, nearly all of the available oxygen is required to support basal metabolism, and the climbing rate near the summit drops to 2 m/min. Changes in healthy individuals at high or extreme altitude may be exaggerated; in patients with chronic cardiopulmonary disease, changes may occur at modest elevations.

More than 140 million people worldwide live more than 2500 m above sea level. Of these people, 80 million live in Asia, and 35 million live in the Andean mountains (the major population density lives >3500 m).

The cardiovascular changes at high altitude are influenced by factors like population ancestry and sociocultural determinants, and also adaptation, nutrition, intercurrent infection, exposure to pollutants and toxins, socioeconomic status, and access to medical care.

Barometric pressure

The percentage of oxygen remains constant at 20.93% at high altitude and at sea level; therefore, barometric pressure determines the partial pressure of oxygen (PO₂) in ambient air. Barometric pressure decreases as one rises in altitude and moves toward the poles. Changing positions of the sun in relationship to the equator affects barometric pressure, producing a seasonal atmospheric tide. At sea level (barometric pressure, 760 mm Hg), the PO₂ of ambient air is 159 mm Hg (760 mm Hg X 0.2093). As air passes through the respiratory tract, it is saturated with water vapor, which makes the inspired PO₂ 149 mm Hg ((760 - 47 mm Hg) X 0.2093).

The alveolar partial pressure of oxygen (PAO₂) is calculated as follows:

$$PAO_2 = [(PB - PH_2O) FiO_2] - [PACO_2 (FiO_2 + 1 - FiO_2/R)],$$

PB is the ambient barometric pressure, PH₂O is the pressure water vapor exerts at body temperature, FiO₂ is the fraction of inspired oxygen, PACO₂ is the alveolar partial pressure of carbon dioxide, and R is the respiratory exchange ratio.

Humans have shown an ability to adapt for short periods to a barometric pressure one third that of sea level on Mount Everest (8848 m [about 29,000 ft]) without supplemental oxygen. At that elevation, the calculated PAO₂ is 35 mm Hg, and the PaO₂ is 28 mm Hg. Humans can permanently live at 5100 m (16,700 ft), which has pressure approximately one half that of sea level. Although cold, low humidity, increased solar radiation, and poor economic conditions limit the ability to survive at high altitude, hypoxia is the most important factor.

Changes in Oxygen Transport

At sea level, the PO₂ available in the atmosphere and that required by mitochondria are large. At each stage of the oxygen transport system, PO₂ decreases; this disease is figuratively called the oxygen cascade.

At high altitudes, the decrease in barometric pressure reduces the amount of oxygen initially available in the environment, making the slope of the cascade considerably less steep than it otherwise is. Mechanisms that compensate for the decreased availability of oxygen in the

environment include changes in the intracellular enzyme systems to allow them to function at low levels of oxygen and changes in the oxygen transport system to increase the amount of oxygen delivered. The latter is the primary compensatory mechanism.

Changes occur at all levels of the oxygen transport system, namely, ventilation, pulmonary diffusion, circulation, and tissue diffusion.

A slight increase in ventilation is first noted on ascent above 1524 m (5000 ft). At rest, this increase is manifested primarily as an increase in the tidal volume. With exercise, both the tidal volume and the respiratory rate increase. The effect of hyperventilation is to decrease PaCO_2 , increasing PAO_2 . This is the most important form of early acclimatization to high altitude. The hypoxia-induced increase in minute ventilation occurs shortly after the person's arrival at altitude and increases during the first week. Minute ventilation later decreases, but it remains above values at sea level.

An increased hypoxic ventilatory response is an important means of acclimatization for the resident at sea level who aspires to participate in activities at high altitude. Mountain climbers with an increased hypoxic ventilatory response have a superior capability to climb to great heights, presumably because of the increased availability of alveolar oxygen. This capacity may also have a downside. A low hypoxic ventilatory response has been implicated in acute mountain sickness, excessive polycythemia, and low birth weight.

Stimulation of the carotid bodies mediates hyperventilation. With acute exposure, ventilation does not notably increase below 3000 m (9840 ft). This situation corresponds to an alveolar oxygen tension of 60 mm Hg. However, after 4 days of exposure to even modest increases in altitude, ventilation is consistently greater than normal ventilation at sea level. After a person acclimatizes, hyperventilation may occur at a PaO_2 as high as 90 mm Hg. The hypoxic ventilatory response persists for the resident at sea level that remains at high altitude. At extreme altitudes, marked respiratory alkalosis develops to maintain an alveolar oxygen tension of more than 35 mm Hg. In a decompression chamber with conditions equal to those at Mount Everest, PaCO_2 is 8 mm Hg.

In contrast, the native high-altitude resident has a blunted hypoxic ventilatory response, or is desensitized, to hypoxia. Improved oxygen usage in the peripheral tissues with decreased ventilatory effort has been postulated as an explanation for this phenomenon. Studies of high-altitude residents showed that, for desensitization to occur, the exposure to high altitude must occur in early childhood and last several years. The decrease in hypoxic ventilatory response is first noted after 8 years of age. At the same time, vital capacity correspondingly increases. After desensitization to hypoxia has occurred in the high-altitude resident, it persists for years, even if the person returns to sea level. Offspring of lowlanders born and raised at high altitude have the same phenomenon as that of native highlanders. The native highlander hyperventilates compared with the lowlander, and the high-altitude resident hypoventilates compared with the newcomer to altitude. Therefore, native high-altitude residents can perform a given physical activity with a relatively small ventilatory requirement; hence, they have less dyspnea than others do. This advantage increases their capacity to perform work at high altitude.

At sea level, the alveolar-arterial (A-a) gradient is 6-17 mm Hg. This gradient may limit exercise by the newcomer to high altitude even if he or she hyperventilates. The development of notable arterial desaturation during exercise suggests this possibility. The native high-altitude resident

has a pulmonary diffusion capacity 20-30% higher than that of a sea-level resident. This capacity helps maximize gas exchange in the alveoli. Changes in the configuration of the chest, anatomic changes of the lungs to increase the surface area of the alveoli, and an improved ventilation-perfusion ratio owing to pulmonary hypertension have been offered as possible explanations for this finding.

Exposure to high altitude has important implications for the cardiovascular system. On initial ascent, sympathetic activity markedly increased, resulting in an initial increase in heart rate and cardiac output. However, after prolonged exposure, maximal oxygen uptake decreases, stroke volume is lowered, and cardiac output falls below sea-level values. The reduction in stroke volume is thought to be secondary to decreased ventricular filling. Exercise markedly reduces maximum cardiac output; this effect is more pronounced in visitors than in natives.

A decrease in coronary blood flow by 32% has been observed after 10 days at 3100 m (10,200 ft). However, no evidence of myocardial ischemia is observed. This finding is presumably due to increased extraction of oxygen from coronary arterial blood and reduced oxygen requirements secondary to decreased cardiac work. Left ventricular dysfunction has been suggested; however, echocardiographic indices of left ventricular contractility are normal and chamber sizes are reduced at altitude.

In a study, it was found that increased pulmonary artery pressure in association with exercise and altitude hypoxia did not cause left ventricular diastolic dysfunction. The authors concluded, "Ventricular interaction seems not to be of hemodynamic relevance in this setting." There is significant right ventricular wall thickness and decreased ejection fraction measured on MRI scans in children with high altitude pulmonary hypertension.

With increasing hypoxia, the maximum heart rate decreases 1 bpm for every 130 m (about 430 ft) above 3100 m (10,200 ft). The decreased cardiac output, stroke volume, and exercise capacity noted at high altitude may be due to decreased preload secondary to a reduction in plasma volume associated with a person's arrival at high altitude.

Changes in the ECG after ascent to high altitude have also been described. Right-axis deviation, right precordial T-wave inversion from a normally upright adult T wave, and T-wave changes in the left precordial leads have been described in mountaineers. ECGs of immigrants to high altitude demonstrate an increase in right ventricular hypertrophy with increased duration of high-altitude residence. Loss of normal circadian rhythm and QTc prolongation have been described in both infants and adults.

In general, systemic blood pressure at high altitude is slightly lower than it is at sea level. This difference is thought to be secondary to the vasodilatory effects of hypoxia on the systemic vascular smooth muscle. The incidence of hypertension at high altitude has been reported to be less than that the rate at sea level.

The final step in the oxygen cascade is the diffusion of oxygen from the capillaries to the mitochondria. For understandable reasons, this step has not been extensively studied at high altitude. Increases in the capillary density and decreases in the size of muscle fibers combine to shorten the distance over which oxygen must diffuse. In several species of animals, this response appears to help them adapt to high altitude, but it does not appear in humans after 40 days of marked hypobaric exposure.

Oxygen-hemoglobin Dissociation Curve

Tissue PO_2 varies little over a PAO_2 range of 70-100 mm Hg. As might be expected at high altitude, a PAO_2 of 40-70 mm Hg is associated with a rapid unloading of oxygen for small changes in oxygen tension. Some have suggested that increased oxygen affinity or a leftward shift on the oxygen-hemoglobin dissociation curve may be beneficial at high altitude. As with fetal hemoglobin, a leftward shift facilitates the loading of oxygen in a hypoxic environment. Others have suggested that a rightward shift may increase the ability of the blood to unload oxygen at the tissue level.

Studies at 4520 m (14,830 ft) have demonstrated that the curve shifts to the right under standard laboratory conditions (pH 7.40 and partial pressure of carbon dioxide [PCO_2] of 40 mm Hg) because of an increase in 2,3-diphosphoglycerate. However, in vivo, the respiratory alkalosis associated with high-altitude hyperventilation results in a leftward shift on the curve. Therefore, the actual PO_2 at 50% oxygen saturation (P50) is not significantly different between sea level and at altitude.

The Mount Everest Medical Expedition revealed a progressive leftward shift at high altitudes as the respiratory alkalosis increased. This effect improves oxygen loading in the lungs.

At each stage of the oxygen transport system, considerable changes occur to facilitate oxygen delivery.

Hematologic Changes

No less important than the transport system is the transport vehicle, namely, the RBC. During the first 1-2 weeks at high altitude, plasma volume decreases, raising the hemoglobin concentration by 1-2 g/dL. In addition, within hours of exposure to altitude, RBC production increases because production of erythropoietin is heightened. However, the overall response is slow, taking months to reach equilibrium.

The degree of polycythemia is directly related to the altitude, up to an elevation of 3660 m (12,000 ft). Above this altitude, the hemoglobin concentration increases rapidly. However, if the systemic arterial saturation falls below 60%, erythropoietic activity decreases. In subjects living at 4540 m (14,900 ft), total blood volume gradually rises from 80 to nearly 100 mL/kg, a change that represents an increase in RBC volume as plasma volume decreases.

Monge disease (chronic mountain sickness) is associated with excessive erythropoiesis.

Polycythemia is associated with hyperviscosity and a decline in oxygen transport. An additional rise in hemoglobin concentration is observed with age at high altitude. At high altitude, climbers with polycythemia have reduced maximal oxygen consumption, even when they breathe 100% oxygen. This observation suggests that the peripheral extraction of oxygen from blood is limited by its reduced flow. Phlebotomy and hemodilution experiments in mountain climbers and autologous RBC transfusions in athletes have not yielded information about the ideal hematocrit for any given altitude.

The platelet count decreases by 7% after 2 days at 2990 m (9800 ft) and by 25% after 2 days at 5370 m (17,600 ft). Some suggest that exposure to high altitude induces a hypercoagulable state in humans. Increased fibrinogen levels and a decreased clot lysis time were noted in 38 soldiers living at high altitude for 2 years, as compared with control subjects at sea level.

Soldiers with clinical evidence of pulmonary artery hypertension had somewhat low levels of fibrinogen, high levels of platelet factor III, and increased platelet adhesiveness. This evidence

suggests that conversion to fibrin, and possibly platelet deposition, were occurring in these subjects with pulmonary hypertension. Similar studies of the coagulation status of patients with cyanotic congenital heart disease have been conducted. The Operation Everest II project performed in a hypobaric chamber showed no changes in coagulation factors.

Metabolic Changes

Most visitors to high altitude notice some initial weight loss. This loss has been attributed to reduced dietary intake, enhanced water loss, and loss of stored body fat. Anorexia is a common complaint of visitors to even moderate altitude. At high altitude, appetite and caloric intake decrease dramatically in unacclimatized persons. They have distaste for fat and prefer sweets. Fluid losses result from the insensible water losses associated with hyperventilation and low humidity, as well as diuresis induced by hypoxia and the cold environment.

Adaptation and Acclimatization

Some residents of newly settled high-altitude communities in the United States may be at increased risk for problems in adapting to high-altitude living. Unlike natives from older communities in the Andes or in Tibet, they have not been genetically selected for high-altitude living.

Chronic hypoxia, pulmonary venous hypertension, and increased pulmonary blood flow can each markedly increase pulmonary pressures in many genetically susceptible individuals, and these factors may be additive. At sea level, 25-30% of adults with critical mitral stenosis develop severe pulmonary hypertension. Among those with a congenital absence of the pulmonary artery and increased flow to the other lung, 19% develop severe pulmonary hypertension. Although pulmonary artery pressures are elevated, this change does not necessarily cause pulmonary vascular disease.

The 20-25% of individuals who respond to various stimuli in this fashion at sea level have been called hyperreactors. In such patients, the minimal chronic hypoxia that is found at even moderate altitude may prime the pulmonary vascular bed and provoke a hyperreactive response to cause a further increase in hypoxia, increased pulmonary blood flow, or pulmonary venous hypertension. In such individuals, the current practice is to correct clinically significant cardiac lesions at an early age to allow the pulmonary artery pressures to regress if continued residence at altitude is contemplated.

Acute Mountain Sickness

Symptoms of AMS occur in nearly everyone if the ascent to altitude is too rapid. The marked variability in symptoms is characteristic of the disorder. Although some experience only minor inconvenience, for others, the symptoms are incapacitating. The symptoms of AMS have been known for many years and were described in 1881 by the physician Jacottet on Mont Blanc, "I was unable to sleep and passed so bad a night that I would not wish it on my worst enemy." Another early description from South America graphically portrays other symptoms in a severely affected altitude sojourner: "I got up and tried once more to go on but I was only able to advance one or two steps at a time, and then I had to stop, panting for breath, my struggles alternating with violent fits of nausea. At times I would fall down, and each time had greater difficulty rising; black specks swam across my sight; I was like one walking in a dream, so dizzy and sick that the whole mountain seemed whirling about me...As I got lower...I improved."

A consensus conference was held during the 1991 Hypoxia and Mountain Medicine Symposium at Lake Louise, Canada to define the various altitude syndromes. 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 sleeping."

AMS is defined by its symptoms, but the exact cause of AMS is still unknown. Cerebral edema may play a role.

Incidence

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 7,000-8,000 ft (2130-2440 m), whereas most unacclimatized persons ascending to 10,000 ft (3,050 m) or higher experience at least a few symptoms.

In a large study of tourists visiting Colorado, 71% had at least some symptoms of AMS after arrival at altitudes of 6900-9700 ft (2100-2960 m). Other studies of various altitudes generally confirm the conclusion that AMS is related to the rate of ascent and the altitude reached. Individuals with a history of altitude illness may tolerate ascent better if the rate of ascent is slowed or if they spend a day or two acclimatizing at an intermediate altitude. In some studies, women had more symptoms than men.

Prediction of AMS

A previous history of AMS suggests susceptibility to the syndrome and the likelihood of recurrence with reascent. However, accurately predicting who will develop AMS is impossible. Some studies have shown that individuals with a lower vital capacity and lower hypoxic ventilatory response are more likely to experience altitude illness.

Pathophysiology

The exact mechanism by which hypoxia causes AMS is still unknown. Hypoxia leads to increased cerebral blood flow, elevated hydrostatic capillary pressure, capillary leak, and, finally, edema. One study suggested that hypoxia stimulates increased cerebral blood flow, resulting in vasogenic cerebral edema. Another study suggests that AMS develops in people who cannot compensate for brain swelling. People with a greater ratio of cerebrospinal fluid (CSF) to brain volume are less likely to develop AMS because the swelling brain is able to displace the CSF. Conversely, those with lesser CSF to brain volume ratio have limited space for compensation of brain swelling and are prone to AMS. The role of fluid retention in the pathogenesis of AMS remains uncertain. Secretion of antidiuretic hormone and atrial natriuretic factor is altered in AMS and may contribute to vasogenic edema.

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 (300-900 m) usually is sufficient to improve symptoms. Supplemental oxygen, although rarely available in sufficient quantities, also effectively relieves symptoms of AMS.

Pharmacological Treatment of AMS

Acetazolamide (Diamox) is effective both for the prevention and for the treatment of AMS. A report demonstrated that 250 mg of acetazolamide every 8 hours dramatically reduced symptoms of AMS compared to people taking a placebo during a stay at the 12,800-ft (3,900-m) summit of Mount Evans, Colorado. Others have confirmed these findings, founding 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 1 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 acetazolamide.

In one report stated that relatively large doses of glucocorticoids can be effective in preventing AMS; however, they are usually reserved for more severe cases of AMS and acute cerebral edema.

The over-the-counter herbal supplement Ginkgo biloba has gained interest in AMS prophylaxis, primarily due to its low adverse effect profile. Although early studies were promising, more recent ones do not support the use of Ginkgo biloba. Some studies demonstrated that Ginkgo biloba was no better than placebo in prophylaxis of AMS. As such, the mainstay of pharmacologic treatment remains acetazolamide and dexamethasone.

Portable hyperbaric bags (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.

Sleep at High Altitude

Most newcomers to altitude frequently report difficulty 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 already exhausted climbers.

Frequent nighttime awakenings and arousals represent the major disruptors of high-altitude sleep. A distinction must be made between an arousal and an awakening. Sleep stages traditionally have been scored on the basis of 30-second epochs. Using this strategy, an awakening is scored on the sleep record when half of the standard epoch is scored as wake

time. An arousal, in contrast, is defined as a 2- to 5-second period of wakefulness within the epoch.

An awakening may be sufficient for the person to remember the next day, while an arousal is not. Despite the transient and unremembered nature of arousals, they serve to dramatically impair daytime performance, especially if they occur frequently.

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 8040 m, 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 (7620 m, 282 mm Hg).

Even those people with the fewest arousals had more than 1 arousal from sleep every minute, while more severely affected individuals had 3-4 arousals each minute. Frequent arousals cause sleep fragmentation, which, in turn, impairs daytime performance, even without concomitant hypoxia. Arousals ordinarily are not remembered the next morning; however, the effects are similar to hypoxia, including altered judgment and performance. Often, the affected person is unaware of these alterations.

Periodic breathing is a common breathing pattern during sleep at high altitude. More than 100 years ago, periodic breathing pattern was described which consists of a series of 3-5 breaths followed by a short respiratory pause, or apnea. Nearly all sojourners to high altitude demonstrate this breathing pattern, but the pattern is far less common among highland Sherpas, who have a blunted hypoxic ventilatory response.

The length of nighttime periodic breathing episodes is related, in part, to a person's ventilatory drive; those with the strongest hypoxic ventilatory response have more frequent episodes of periodic breathing. Periodic breathing may occur in all sleep stages, including rapid eye movement (REM) sleep; however, at very high altitude, the time spent in slow wave and REM sleep is markedly reduced.

Changes in sleep state, as well as conflicting effects of hypocapnia and hypoxia on the peripheral chemoreceptors, lead to a destabilization of the respiratory control system, which is responsible for the periodic breathing observed at high altitude. A sophisticated model of periodic breathing was developed and it suggested that increases in chemoreceptor gain (such as occurs in those with a strong hypoxic ventilatory response) lead to destabilization of the respiratory system and periodic breathing. This model further predicts that cycle length (time from one apnea to the next) decreases as altitude increases. Findings from studies on Mount Everest generally confirm this prediction, although cycle time decreased less than predicted by the model.

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 arousals.

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 (7620 m) 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 (acetazolamide) decrease nocturnal periodic breathing, improve arterial oxygen saturation, and ameliorate daytime symptoms of AMS.

High-Altitude Pulmonary Edema

HAPE is a serious and potentially life-threatening manifestation of altitude illness. With a report in the *New England Journal of Medicine* in 1960, the medical community began to recognize this unusual form of pulmonary edema and confirmed that heart failure was not the cause of the edema.

Signs and Symptoms

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, the 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.

Diagnosis

The diagnostic criteria for HAPE are at least 2 symptoms and 2 signs in the setting of a recent gain in altitude. Symptoms include dyspnea at rest, cough, weakness or decreased exercise performance, and chest tightness or congestion. Signs include rales or wheezing in at least 1 lung field, central cyanosis, tachypnea, and tachycardia.

A chest radiograph 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

Chest radiographs are useful to confirm the diagnosis of HAPE and may show abnormalities, even 24-48 hours after descent to sea level. 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.

Incidence

The incidence of HAPE is affected by factors such as rate of ascent, age, sex, physical exertion, and, most importantly, individual susceptibility. The reported incidence ranges from 0.1%

among 143 skiers traveling to 8,200 ft (2,500 m) in Colorado to 4.5% at 14,000 ft (4,270 m) among trekkers in Nepal. On Mount McKinley in Alaska, incidence is as high as 20-33%. Early or subclinical cases of HAPE occur much more frequently than full-blown cases. Children, but not infants, appear to be more susceptible than adults. Males are more likely to develop HAPE than females, but the reasons are unclear.

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.

Pathophysiology

The exact pathophysiology of HAPE is hampered by the lack of a good animal model. Any model 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).

Factors leading to a low partial pressure of oxygen (PO₂), such as exercise, sleep, or a low ventilatory response to hypoxia, increase the likelihood of developing HAPE. Alterations in the sympathetic nervous system are also believed to contribute to the development of HAPE.

Recent evidence suggests that a defect in sodium transport across the alveolar epithelium may be important in susceptible individuals.

Alveolar hypoxia leads to hypoxic pulmonary vasoconstriction following ascent to high altitude. The extent of vasoconstriction is highly variable among individuals, probably due to different genetic characteristics. Individuals susceptible to HAPE have more severe pulmonary arterial hypertension than normal at altitude; however, not everyone with exaggerated hypoxic pulmonary vasoconstriction develops HAPE.

Many years ago it was proposed that the development of HAPE was an overperfusion mechanism that caused uneven hypoxic pulmonary vasoconstriction which resulted in lung areas with decreased blood flow while other areas receive excessive flow. Leakage of edema fluid occurs in these overperfused lung regions. Magnetic resonance imaging studies from 2005 by confirm the increased blood flow heterogeneity in individuals susceptible to HAPE.

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. These inflammatory markers are now felt to be an epiphenomenon rather than a direct cause of the pulmonary capillary leakage in HAPE.

It has been suggested that HAPE results from a rupture of pulmonary capillaries subjected to high wall stresses from high pressure in the vessels. The nonhomogeneous vasoconstriction would allow high pulmonary artery pressures to be transmitted to pulmonary capillaries in overperfused areas of the lung.

Clearance of fluid from the alveoli and interstitial space is important in the prevention and resolution of pulmonary edema. The epithelial sodium channel (ENaC) appears to be the most important regulator of this process. Both beta agonists and steroids up-regulate the ENaC ion channels within the alveolar epithelial cells. It has been shown that inhaled salmeterol is useful

in preventing HAPE. In 2004, a study found a 60% reduction in the mRNA for the epithelial sodium channel in humans following acute exposure to high altitude.

Treatment of HAPE

Both the overperfusion and stress failure models for HAPE imply that a reduction of the excessive hypoxic pulmonary vasoconstriction is essential 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 (300-900 m) 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 with 10 mg nifedipine followed by 20 mg of slow-release nifedipine every 6 hours showed improvement in oxygenation and overall condition, even without descent to lower altitude. Other vasodilators may also decrease pulmonary artery pressure and be useful in treating HAPE. Reliance on these medications should not delay early and rapid descent.

One report stated that calcium channel blockers and phosphodiesterase type 5 inhibitors are effective for treating acute pulmonary edema.

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

The best treatment is prevention of HAPE by gradual ascent and early recognition of HAPE symptoms. Nifedipine and phosphodiesterase-5 inhibitors are useful in preventing HAPE among susceptible individuals by lowering pulmonary artery pressure and salmeterol through their action on ion channels.

High-Altitude Cerebral Edema

HACE is an extreme form of mountain sickness. The Lake Louise definition 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 both mental status change and ataxia in a person without AMS." Without prompt treatment, further neurological deterioration and death are likely.

Although many cases of HAPE occur without coexisting HACE, most cases of HACE have coexisting HAPE. The incidence of HACE is considerably less common than HAPE. Whether males are more likely to develop HACE than females remains unclear, although more cases of HACE in males have been reported.

Signs and symptoms of HACE may progress rapidly (within 12 hours) 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.

It has been suggested that cytotoxic cellular edema of the brain from hypoxia caused many of the signs and symptoms of both AMS and HACE. It has also been suggested that HACE was caused by vasogenic edema resulting from increased cerebral blood flow, causing leakage of fluid into the brain. Other studies 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 4 mg 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 (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 Populations at High Altitude

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 persons 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 disease. During exercise testing at 10,150 ft (3,100 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 5,280 ft (1,600 m). Thus, ascent to altitudes of 10,000 ft (approximately 3,000 m) has little direct effect on myocardial ischemia but may produce symptoms by increasing heart rate and blood pressure during submaximal exercise.

Despite the increase in cardiac symptoms following rapid ascent to high altitude, the increased risk for cardiac death is low. In a large survey of trekkers in Nepal, no deaths from cardiac disease were reported, although several individuals required evacuation for cardiac problems. Other studies conducted at moderate altitudes in the Colorado Rocky Mountains among unacclimatized elderly individuals suggest a relatively low risk. Due to the effects of altitude on patients with cardiovascular disease, it is suggested that an evaluation of a patient with heart disease (including performing a pre-ascent exercise test) be done prior to trekking at high altitude.

With sufficient time for acclimatization, patients with coronary heart disease are likely to experience decreased symptoms because of a lower blood pressure. With long-term exposure

to altitude, coronary artery disease mortality rates in these individuals actually are lower than that observed at sea level.

Pulmonary Disease

COPD

Shortness of breath occurs in everyone, including those without heart or lung disease, after ascent to altitude. Even at sea level, patients with chronic obstructive pulmonary disease (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. In a study, patients with COPD without evidence of cor pulmonale were exposed to 6300-ft (1920-m) altitude.

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 52 mm Hg. In these patients, they researchers 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. Another report stated that impairment in gas exchange in COPD patients is significant in altitude-related hypoxemia.

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 residents.

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 improve altitude symptoms. Prior to traveling to high altitude, persons with primary pulmonary hypertension should consult a physician familiar with altitude problems who can evaluate the potential risks. Primary pulmonary hypertension may be more common among persons living at high altitude, and these individuals should be encouraged to consider moving to lower altitude.

Asthma

Asthma is a common disorder affecting many young, active individuals; therefore, a significant number of altitude sojourners have asthma or reactive airways. 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 doing as well or 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 greater, 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.

Air Travel

As global travel becomes more readily available and affordable, more individuals with preexisting cardiac and pulmonary problems are traveling by air. Pressurized cabins on airliners increase the barometric pressure 385-445 mm Hg higher than the outside ambient pressure. Commercial aircraft fly at altitudes of 10,000-60,000 ft (3,048-18,288 m), thus acutely exposing passengers to high altitude. A study measured the cabin altitudes in more than 200 commercial flights. In these measurements, the median altitude was 6214 ft (1894 m), with an average cabin altitude of 5673 ft (1724 m) and a standard deviation of 2019 ft (615 m). In this study, the maximum altitude observed was 8915 ft (2717 m). Newer aircraft models had significantly higher cabin altitudes than those of older planes.

Healthy individuals readily adapt to these altitudes, but those who are hypoxic at sea level may require supplemental oxygen during their flight. Without supplemental oxygen, individuals with COPD develop significant arterial oxygen desaturation. In one study, the arterial PO_2 decreased from 68 ± 8 mm Hg to 51 ± 9 mm Hg; in another study, the arterial PO_2 decreased from approximately 72 to 47 mm Hg. Both of these studies indicate the need for in-flight oxygen supplementation for these patients. An altitude stimulation test is useful for estimating the flow of oxygen required during flight. In this test, measurements of arterial blood gases are performed while the patient breathes a hypoxic gas mixture.

Sickle Cell Disease

Many genetic variations occur in the hemoglobin molecule. Some individuals having hemoglobin with an unusually high oxygen affinity may have improved altitude acclimatization and function. 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 occur.

Approximately 6-8% of black people in the United States carry at least 1 abnormal hemoglobin gene. 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.

Providing supplemental oxygen to those individuals with sickle cell anemia during aircraft flights may be considered. 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 8,000-10,000 (2,440-3,048 m) without difficulty, although a few may become symptomatic. Although most persons with sickle cell disease are

of African American ancestry, sickle cell trait, and even sickle cell crisis, may occur in white people.

Chronic Mountain Sickness or Monge Disease

An increase in RBC production and resulting polycythemia are normal responses to high altitude. However, some high-altitude residents become severely symptomatic as a result of excessive polycythemia. This condition has been called chronic mountain sickness, or Monge disease.

Symptoms of Monge disease range from diminished mental and physical capacity to headaches, personality changes, unconsciousness, and coma. Healthy men at 4540 m (14,900 ft) have hematocrits of approximately 60% and hemoglobin values of 19 g/dL. Patients with Monge disease may have hematocrits as high as 84% and hemoglobin concentrations of 28 g/dL. Normal arterial saturation at that altitude (81%) may fall as low as 60% in affected individuals.

Periods of hypoventilation and arterial desaturation during sleep, as well as small tidal volumes, were described in residents of Leadville, Colorado, with excessive polycythemia.

In theory, this desaturation further decreases both alveolar and systemic oxygen tensions and stimulates RBC production. Blood viscosity increases with the hematocrit, which in turn decreases cerebral blood flow. The worsened hypoxemia due to hypoventilation and the reduced cerebral blood flow combine to cause symptoms. Phlebotomy improves symptoms and oxygen saturations, and it lowers pulmonary artery pressure. Similar increases in erythropoietin values, hematocrits, and blood viscosity have been described in patients with cyanotic congenital heart disease.

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