Neurology and altitude illness

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Summary

Problems at altitude are most often thought of in trained athletes summiting extremes of elevation. A more common group that needs consideration is the average person with obstructive sleep apnea who must travel to high altitudes for business or pleasure. While the altitudes involved are not likely to be as extreme as for those athletes climbing peaks like Mt. Everest, the increases in elevation may present difficulties for patients, especially if overnight stay is expected. The pathophysiology of altitude-related CNS, respiratory, and sleep disorders is discussed along with treatment options.

Patients are commonly exposed to high altitudes for recreational and vocational reasons. This article discusses CNS problems associated with altitude and its treatment.

What is meant by altitude and how does it affect oxygen levels?

Altitudes are categorized as low, moderate, high, very high, and extreme. High altitudes begin at 2,400 meters, very high at 4,000 meters, and extreme at 5,500 meters. Although oxygen remains a constant 21%, altitude-related barometric pressure drops result in decreased available oxygen. Sea level barometric pressure is 760 mm Hg. At a high altitude of 4,000 meters (the elevation of Pikes Peak, Colorado), barometric pressure decreases to 440 mm Hg, and on Mt. Everest (approximately 9,000 meters), 250 mm Hg. With 21% fractional oxygen at all altitudes, the partial pressure of oxygen at sea level is 149 mm Hg, with Mt. Everest only 42 mm Hg.

What happens to people at high altitudes?

The effects of hypoxia depend on the rate of ascent. An 1862 balloon ascent was made rapidly to approximately the same altitude as the summit of Mt. Everest,¹ resulting in catastrophic paralysis. One of the aeronauts was able to use his teeth to pull the pressure release cord and cause the balloon's descent. The aeronauts fully recovered upon landing, although the precise cause for their affliction is unclear. In modern times, ascent by foot, wheeled vehicle, or pressurized aircraft is common and resulting altitude illnesses include acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE).

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These conditions do not generally occur until 2,500 meters altitude or greater. Studies have attempted to determine who is susceptible to altitude illness; several risk factors have been identified, but none is a reliable predictor.²⁻⁴ One modifiable risk factor is clear: if the rate of ascent is slowed, the probability of altitude illness decreases. AMS develops hours to days after reaching altitude, and a headache is required for the diagnosis. Other symptoms include fatigue, weakness, nausea, vomiting, and anorexia. HACE is a continuation of the CNS changes occurring with AMS and includes ataxia, lassitude, and an altered level of consciousness that terminates in coma and death.

Headache in AMS may be caused by the hypoxic induction of nitric oxide production in the brain and activation of the trigeminovascular reflex,^{5,6} an inflammatory response,⁷ and increased reactive oxygen species formation.⁸

Hypoxia also causes energy failure in vascular basement membranes, leaky endothelium, and vasogenic cerebral edema. This leads to increased intracranial pressure, decreased cerebral blood flow, generalized cerebral ischemia and decreased level of consciousness, coma, and finally death.

Hyperventilation-induced hypocarbia may also cause cerebral vasospasm; therefore, dysfunctional cerebral autoregulation has been studied as a possible contributing factor in AMS and HACE (using transcranial Doppler ultrasound)⁹ in Sherpas (who live at altitudes between 3,000 and 4,300 meters) and in climbers. Sherpas demonstrated maximum cerebral arterial vasodilation, as did most climbers, showing that the majority of humans at altitude, regardless of altitude of residence, have fully dilated vessels, making it unlikely that disordered autoregulation is a contributing factor to either AMS or HACE.

Low oxygen tension produces lung tissue hypoxia and an increase in sympathetic activity, impaired nitric oxide synthesis, pulmonary vein constriction with increased pulmonary capillary pressures, and increased microvascular permeability, causing HAPE.^{10,11} Occurring at 2,500 meters altitude or greater over 2–4 days, symptoms include dyspnea at rest, cough, and exercise intolerance compared to the previous days. Development of this syndrome does not protect the patient from AMS or HACE, and both pulmonary and cerebral symptoms can occur. This condition is differentiated from high-altitude cough by absence of dyspneic symptoms.

Altitude affects other organs as well. Responding to the respiratory alkalosis, kidneys secrete bicarbonate, producing a compensated respiratory alkalosis. Catecholamine release increases blood pressure and heart rate, promoting diuresis and volume contraction. Volume contraction is often concurrent with self-inflicted dehydration by a climber not consuming fluids due to the weight of water on long mountaineering treks and desiring to minimize urination in an extremely cold environment. Increased insensible losses from hyperventilation and the cold dry air increase volume loss.

Treatment of altitude-induced illnesses

The best prevention is slow ascent above 2,500 meters, no more than 500 meters per day. One important factor also seems to be the altitude at which one sleeps rather than just the ascent during waking hours,¹² thus daytime sojourns to higher elevations may be better tolerated. The best treatment for all altitude illnesses is immediate descent by at least 1,000 meters.

Common prophylaxis for AMS and HACE is acetazolamide BID or dexamethasone. Ibuprofen has been studied for prophylaxis, but is controversial and not recommended at this time, although it does treat high-altitude headache presumably due to its anti-inflammatory properties.^{13,14} Treatment of AMS and HACE involves different doses of the same medications and details of the treatment for altitude illnesses are well-described.¹² Of special note is that nifedipine, commonly used for HAPE prophylaxis, should not be used if the patient also has AMS/HACE, as this drug may worsen cerebral edema.

Altitude effects on sleep

The principal groups that spend large amounts of time at high and extreme altitudes are mountaineers and military personnel. Mountaineers include hobbyists, professional climbers, and

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search and rescue personnel. Military actions at high altitudes are common.¹⁵ These 2 groups have done the most work on sleep effects at altitude, although others work at altitude as well.

During sleep, the previously discussed hypoxemia suppresses ventilatory drive to the point of apnea. Carbon dioxide levels increase, stimulating respiration, which (with hypoxia) produces hyperventilation, and the cycle repeats, producing periodic breathing.

Respiratory control involves both central and peripheral mechanisms. The brainstem contains chemoreceptors in the retrotrapezoid nucleus of the pons. These cells have direct input to the respiratory control pattern generators of the pons and medulla, which are sensitive to changes in CO_2 .¹⁶ Other nuclei involved with chemoreception are dorsal raphe nuclei, the locus ceruleus, nucleus tractus solitarius, and orexinergic hypothalamic nuclei.¹⁷ The carotid body receptors at the bifurcation of the carotid arteries are more sensitive to changes in arterial oxygenation, but sense arterial CO_2 content as well. The interplay between central and peripheral chemoreception adjusts the respiratory drive via a concept known as “loop gain.”¹⁸ Loop gain consists of 3 parts: the controller (CNS respiratory pattern generators modulated by central and peripheral chemoreception), the actual change in pO_2 or pCO_2 , and the delay due to circulatory time from the lungs (point of change) to the central and peripheral sensors. At altitude, hypoxia-induced hyperventilation and subsequent hypocarbia induces a loop gain abnormality (gain greater than one) causing ventilatory instability: a subsequent oscillatory effect that produces periodic breathing.

What are the sleep effects of altitude on normal subjects?

Because there are no sleep laboratories located at extreme altitudes, most of the available studies have been performed in altitude chambers with altitude simulated by lowered barometric pressures. It is well known that at altitude, virtually everyone exhibits periodic breathing and complains of difficulty maintaining sleep/poor sleep quality and has a subjective impairment of cognition.

One experiment using 10 volunteers at a simulated altitude of 4,500 meters¹⁹ with an average 78% O_2 saturation in the subjects demonstrated an increased number of awakenings correlating with apneas. Baseline sleep efficiency was 84%, which dropped to 66% at altitude. Minutes of wake time after sleep onset increased from 45 minutes at baseline to a mean of 117 minutes. Total respiratory events were 19 per hour at baseline increasing to 199 per hour at 4,500 meters simulated. During the same experiment, effects on mood were measured, and the patient’s uniformly endorsed changes at altitude consisting of depression, anger, decreased vigor, and increased fatigue.

Altitude chambers cannot completely simulate the environmental factors of actual ascent to extreme altitudes. Under real-world conditions, climbers are also subject to temperatures approaching -40°C , high winds, storms, altitude sickness, and exhaustion/fatigue from the effort of climbing (energy requirements can increase from 2,000 to 4,500 kcal per day). Add to this dry air/increased insensible losses and dehydration (both physiologic and self-imposed). Finally, real climbing does not involve continuous elevation increases. There are many frequent ascents and descents involving varying amounts of time, altitudes, and distances. These factors make climbing quite different from the smooth gradual “ascent” in a hypobaric chamber.

For travelers with preexisting OSAS, their condition may worsen at altitude because of the addition of central sleep apneas to their obstructive apneas.

There are few polysomnographic studies at high and extreme altitudes, which is understandable given the logistical difficulties of getting such equipment in place. Two studies were performed at 4,300 meters and 5,000 meters actual altitude.^{20,21} Both demonstrated deteriorating sleep quality and decreased total sleep time at higher altitudes, along with periodic breathing. A single study was performed at 7,500 meters during an expedition to Mt. Everest. While this expedition (MEDEX2006)²² did not study sleep architecture at the top of Mt. Everest (which is slightly less than 9,000 meters), it provides the only objective look at sleep patterns at extreme altitudes to date.

In MEDEX2006, the baseline apnea-hypoxia index was 5 at 500 meters, at the base camp (5,300 m) it was 138, and at 7,500 meters an increase to 148 was noted. At those altitudes, blood oxygen saturation was noted to be 94%, 71%, and 58%, respectively. Another study during actual ascent was performed to discern subjective sleep quality and psychological function/well-being at high and extreme altitudes.²³ Volunteers were studied at sea level, 4,500 meters, 6,100 meters, and 7,100 meters elevation. This study utilized the Pittsburgh Sleep Quality Index and the Athens Insomnia Scale-8. The results showed increased sleep latency, more frequent nocturnal awakenings, decreased total sleep time, worsened sleep quality, and a general sense of poor daytime function. These objective measures correlated with historical anecdotal reports from climbers. Polysomnographic data were not obtained during those studies.

What are the altitude effects on patients with obstructive sleep apnea syndrome?

Patients with obstructive sleep apnea syndrome (OSAS) frequently travel to moderate and high altitudes for business and pleasure. At low altitudes, patients with OSAS have a loop gain of greater than one¹⁸ and by definition have ventilatory instability. The mechanism is uncertain, but may involve output of a central respiratory pattern generator that fluctuates in response to the increase or decrease in mechanical (airway) resistance during sleep.¹⁷

In 2010, patients with known OSAS were studied at <600 meters elevation and >2,500 meters. They were not given continuous positive airway pressure (CPAP) and were monitored. A significant increase in apneic events, both obstructive and central, as well as frequent nocturnal awakenings and impaired daytime task performance was seen.²⁴

Is there an association between HAPE and OSAS?

Both OSAS and high altitudes²⁵ are associated with periodic breathing. As HAPE is also a high-altitude phenomenon, the possibility of patients with OSAS developing HAPE during travel to altitudes must be considered. A study of healthy subjects suggested that people with more periodic breathing during sleep (such as patients with OSAS) tend to develop HAPE more often than other subjects.²⁶ Another study demonstrated that all patients with OSAS at high altitudes developed subclinical pulmonary edema based on reductions in arterial oxygen saturation, forced vital capacity, and forced expiratory volume in 1 second,²⁷ demonstrating that all patients with OSAS develop HAPE at high altitudes. HAPE prophylaxis would seem reasonable for all patients with OSAS.

What is the best treatment for patients with OSAS at altitude?

For travelers without preexisting sleep-associated respiratory disorders, oxygen was shown to alleviate altitude-associated periodic breathing,²⁸ although the weight of oxygen bottles on

expeditions (as well as the added expense) makes it difficult to use. Acetazolamide treats this problem in extreme altitude climbers without the weight or expense of oxygen.²⁹

For travelers with preexisting OSAS, their condition may worsen at altitude because of the addition of central sleep apneas to their obstructive apneas.³⁰ For those requiring CPAP, continuation of treatment is best; however, since some patients are unwilling or unable to take equipment with them, acetazolamide, 250 mg twice a day, improves sleep-associated respiratory disturbances by decreasing loop gain³¹ and reducing periodic breathing and central sleep apneas by approximately 50% at moderate elevations and 75% at high elevations,³² and also reducing the number of arousals that occur.³² A recent study of patients with OSAS showed a beneficial effect of acetazolamide and autopap combined³³ at altitude.

Therefore, best practice for patients with known OSAS who wish to travel to altitude appears to be using a properly functioning CPAP machine, following good sleep hygiene techniques, taking acetazolamide, and acclimatizing by slow ascent (not possible if traveling from low to high altitudes by airplane).

Although not specifically studied in patients with OSAS at high altitudes, the addition of low flow (1–2 L/min) nocturnal oxygen is helpful in climbers, and may be advantageous in patients with OSAS by further reduction of periodic breathing and central apneas. Any disadvantages of using oxygen in patients with OSAS are eased since if their travel is by vehicle, transport of oxygen bottles will be simple, and if by airplane, they will be traveling to a city where oxygen could be obtained locally. Finally, the use of CPAP in the automatic mode (autopap) with an extended pressure range³⁴ while taking acetazolamide can also be beneficial.³⁵

DISCUSSION

The cerebral, pulmonary, and sleep effects of altitude are well-known but incompletely understood. The best prevention of altitude illnesses in all people is gradual ascent with acclimatization stops and the best treatment remains descent to <2,500 meters, although pharmacologic prevention and treatment exist as well.

For patients with OSAS, good sleep hygiene and continued use of CPAP can be considered the best practice, but could and probably should be supplemented by acetazolamide, nocturnal oxygen, and autopap in order to improve sleep and well-being during overnight travel to altitude.

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