Concise Clinical Review

High-Altitude Medicine

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Medical problems occur at high altitude because of the low inspired P_{O_2}, which is caused by the reduced barometric pressure. The classical physiological responses to high altitude include hyperventilation, polycythemia, hypoxic pulmonary vasoconstriction–increased intracellular oxidative enzymes, and increased capillary density in muscle. However, with the discovery of hypoxia-inducible factors (HIFs), it is apparent that there is a multitude of responses to cellular hypoxia. HIFs constitute a master switch determining the general response of the body to oxygen deprivation. The recent discovery of genetic changes in Tibetans has opened up an exciting area of research. The two major human populations that have adapted well to high altitude, the Tibetans and Andeans, have strikingly different phenotypes. Diseases of lowlanders going to high altitude include acute mountain sickness, high-altitude pulmonary edema, and high-altitude cerebral edema. Diseases affecting permanent residents or highlanders include chronic mountain sickness and high-altitude pulmonary hypertension. Important recent advances have been made on mitigation of the effects of the hypoxic environment. Oxygen enrichment of room air is very powerful. Every 1% increase in oxygen concentration reduces the equivalent altitude by about 300 m. This procedure is used in numerous facilities at high altitude and in a Chinese train to Lhasa. An alternative strategy is to increase the barometric pressure as in aircraft cabins. A hybrid approach combining both strategies shows promise but has never been used. Mines that are being developed at increasingly high altitudes pose great medical problems.

Keywords: hypoxia; oxygen sensing; hypoxia-inducible factors; genetic changes; oxygen enrichment of room air

High-altitude medicine is a large topic with several textbooks and a journal devoted to it. This is a broad review with an emphasis on recent advances in the subject and a discussion of some topics that may be unfamiliar to readers.

BAROMETRIC PRESSURE AND ALTITUDE

The deleterious effects of high altitude are primarily caused by the low inspired P_{O_2}. The moist inspired P_{O_2} is equal to the fractional concentration of oxygen times the barometric pressure minus the water vapor pressure of the body [$P_{I_{O_2}} = 0.2093$ (PB – 47), where 0.2093 is the fractional concentration, PB is the barometric pressure, and 47 mm Hg is the water vapor pressure at 37°C]. The fractional concentration of oxygen is independent of altitude over the range of medical interest. Therefore, the reduced inspired P_{O_2} is determined solely by the fall in barometric pressure.

Figure 1 shows the decrease of inspired P_{O_2} with increasing altitude. The barometric pressure at sea level is 760 mm Hg, and it falls to half of this value at an altitude of 5,800 m on a typical mountain in the Himalayas or the Andes. The relationship between barometric pressure and altitude depends on latitude and the season of the year (1). Near the equator, where most of the very high mountains of the world are located, the barometric pressure at a given altitude is higher than locations far north or south of the equator because the sun mainly warms the air near the equator, and the upwelling of the air creates a larger mass, thus increasing the barometric pressure. One consequence of this is that a climber on Mt. Everest (28°N latitude) is exposed to a higher barometric pressure than a climber on Mt. McKinley (63°N latitude) at the same altitude. The season of the year also has an effect on the barometric pressure because in the summer the sun's rays heat the air more, resulting in a higher column and thus increasing the pressure.

Because of the differences in the pressure–altitude relationship caused by latitude and season, the "standard atmosphere" was introduced as a mean, and it is extensively used by the aircraft industry. There are significant differences between the actual pressure–altitude relationship on most mountains and the standard atmosphere. For example, at the summit of Mt. Everest during the climbing seasons, the barometric pressure is about 253 mm Hg, whereas the standard atmosphere predicts a pressure of 236 mm Hg. This difference significantly affects the maximum oxygen uptake of climbers (1).

PHYSIOLOGICAL RESPONSES TO HIGH ALTITUDE

Classical Responses to High Altitude

Classical responses to high altitude include hyperventilation, polycythemia, hypoxic pulmonary vasoconstriction, changes in oxygen affinity of hemoglobin, increases in oxidative enzymes, and increased concentration of capillaries in peripheral muscle. These responses have been described in detail in many textbooks and are not repeated here.

Recent Advances in Oxygen Sensing

Recently there has been a dramatic change in our understanding of the responses of the body to hypoxia with the discovery of hypoxia-inducible factors (HIFs). The original finding was a protein that bound to the hypoxia response element (HRE) of the erythropoietin (EPO) gene under hypoxic conditions (2). Since then, it has become apparent that HIFs play a critical role in a large number of responses of cells to hypoxia (Figure 2). Indeed, in cellular hypoxia, the transcription of several hundred messenger RNAs is increased, and the expression of an equal number of mRNAs is decreased (3).

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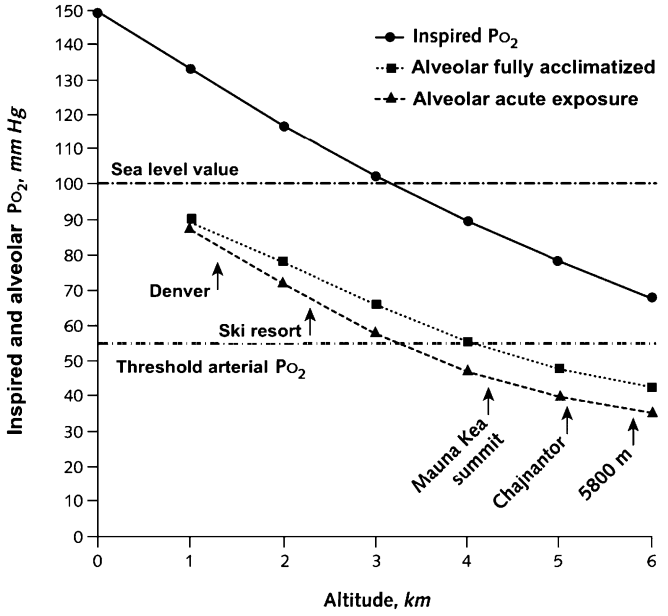

Figure 1. Inspired and alveolar P_{O_2} values at altitudes up to 6000 m. The locations include a typical ski resort village (Aspen, Colorado); the summit of Mauna Kea, Hawaii, where several telescopes are located; Chajnantor, Chile, the site of several radiotelescopes; and an altitude of 5,800 m, where the barometric pressure is half of the sea level value. The *lower horizontal broken line* shows the arterial P_{O_2} below which patients with chronic obstructive pulmonary disease are entitled to continuous oxygen therapy. The values for acutely exposed and fully acclimatized subjects are from Reference 74.

HIFs are transcription factors that respond to the amount of oxygen in the cell. A transcription factor is a protein that binds to specific DNA sequences in a gene and thus allows the flow of genetic information from DNA to messenger RNA. Cellular hypoxia results in an increased concentration of HIF-1α, which then binds to HIF-1β and consequently affects the hypoxia response element. It has been shown that most oxygen-breathing species express these transcriptional factors, indicating that HIFs have been highly conserved. HIF-1 is expressed in very primitive animals, such as the worm *Caenorhabditis elegans*, that do not have specialized respiratory or circulatory systems. The implication is that HIF was initially developed to allow individual cells to survive in low-oxygen environments.

HIFs control genes that have multiple functions throughout the physiological spectrum (Figure 2). These include mitochondrial genes involved with energy utilization; glycolytic enzyme genes influencing anaerobic metabolism; genes associated with vascular endothelial growth factor controlling angiogenesis; genes of nitric oxide metabolism, which is involved with pulmonary vasodilatation; erythropoietin genes affecting red blood cell production; and genes controlling the induction of tyrosine hydroxylase that play a role in the function of the carotid body chemoreceptor. Thus, HIFs constitute a master switch in the general response of the body to hypoxia.

Acclimatization

Acclimatization refers to the array of beneficial changes that occur in the body in response to the hypoxia of high altitude, and it is often used as an example of how the human organism can successfully adapt to a hostile environment. The most important physiological response in acclimatization is hyperventilation. Polycythemia also occurs, although this is relatively unimportant in the lowlander who goes to high altitude for 2 or 3 weeks because the response is so slow. Marked polycythemia, as is sometimes seen in highlanders living in the Andes, can be counterproductive. Hypoxic pulmonary vasoconstriction is not a feature of acclimatization. It confers no advantage and may be a factor in the development of high-altitude pulmonary edema (see below).

There are important misconceptions about acclimatization. Some people who are required to work at high altitude believe that acclimatization can return the body to its sea level condition. This attitude is seen in some astronomers who work in high-altitude observatories, such as those on the summit of Mauna Kea (altitude 4,200 m). These people resist procedures that mitigate the effects of high altitude, such as oxygen enrichment of room air, and argue that they would rather use nature's remedy, which is acclimatization. The truth is very different. As Figure 1 shows, acute exposure to the altitude of Mauna Kea after ascent

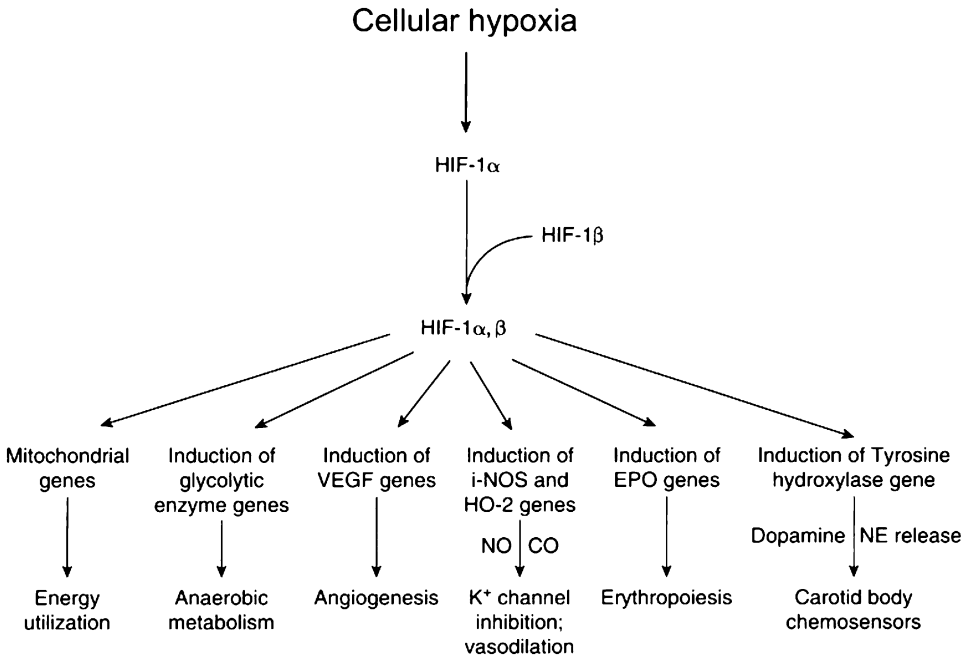

Figure 2. Some of the physiological consequences of an increase in hypoxia-inducible factor (HIF)-1α caused by cellular hypoxia. Adapted by permission from Reference 75. EPO = erythropoietin; i-NOS = inducible nitric oxide synthase; NE = norepinephrine; VEGF = vascular endothelial growth factor.

from near sea level results in an alveolar P_{O_2} of approximately 45 mm Hg. With full acclimatization, the P_{O_2} increases to about 54 mm Hg on average. Full acclimatization takes several days and never occurs for these astronomers because of their work schedules.

Figure 1 also emphasizes the severity of the hypoxia by showing a line indicating an arterial P_{O_2} of 55 mm Hg, which will always be a few mm Hg below the alveolar value. This is the arterial P_{O_2} below which patients with chronic obstructive pulmonary disease are entitled to continuous oxygen therapy under Medicare (4). In other words, if the arterial hypoxemia of an astronomer on Mauna Kea was caused by chronic obstructive pulmonary disease, he would be entitled to continuous oxygen therapy.

Studies have shown that the function of somebody working at an altitude of 4,200 m is not normal (5). There is an obvious reduction in maximum oxygen uptake, and there is evidence that neuropsychological function is also impaired. Indeed, the famous statement by Barcroft in 1925 holds true: "All dwellers at high altitude are persons of impaired physical and mental powers" (6).

GENETIC CHANGES AT HIGH ALTITUDE

Historical Evidence

One of the most important recent advances in high-altitude medicine has been the discovery of genetic changes in Tibetans. Suggestive evidence of these changes has been around for 100 years. For example, in the early 1900s, Himalayan explorers recognized the remarkable exercise ability of Sherpas (who were originally Tibetans) at high altitude, and subsequently these people have made important contributions to expeditions to Mt. Everest, culminating on the first ascent in 1953 when Tensing Norgay Sherpa partnered with Edmund Hillary. More recently, there have been formal studies describing the superior exercise ability of Tibetans under hypoxic conditions (7).

Other physiological changes have also been described. For example, Tibetans and Sherpas have lower hemoglobin concentrations at high altitude compared with Han Chinese and Westerners (8, 9). These lower hemoglobin concentrations are consistent with the reduced prevalence of chronic mountain sickness in Tibetans compared with Andeans (10). Tibetans also exhibit a smaller degree of hypoxic pulmonary vasoconstriction compared with Andeans and other high-altitude populations (11), although some indirect measurements of pulmonary artery pressure do not confirm this finding (12). Consistent with this, Tibetans have higher plasma concentrations of nitric oxide metabolites than North Americans (13). Other features of Tibetans are that the infants have a higher birth weight for the same altitude (10) and that Tibetan newborns have higher arterial oxygen saturations than Han Chinese (14). Thus, many people suspected that Tibetans were genetically different.

Genetic Changes in Tibetans

Beginning in 2010, there was an explosion of new findings, with at least seven different publications from different groups describing genetic changes (15–21). The investigators took different approaches, and only three are briefly summarized here. Beall and colleagues (16) scanned the entire human genome and looked at over 500,000 single-nucleotide polymorphisms (SNPs). They found that eight of these SNPs had variants that were significantly increased in Tibetans. All eight SNPs were on chromosome 2 close to the EPAS1 gene (endothelial PAS domain protein 1), which encodes for HIF-2α. The authors argued that changes in EPAS1 could reduce the erythropoietic response and help to avoid the development of chronic mountain sickness.

Another approach was taken by Simonson and colleagues (19), who focused on a subset of candidate genes thought to have a high probability of being involved in adaptation to high altitude. Tibetans were compared with lowland Asian populations, including those in China and Japan. Ten genes suggesting a strong signal for positive selection were identified, and six of these were related to the HIF system, including EPAS1. Other genes, including EGLN1 and PPARA, were also associated with red blood cell production.

Yi and colleagues (21) took another approach and limited their analysis to 50 exomes of Tibetans (i.e., those parts of the genome formed by all the coding exons). The EPAS1 gene was identified with others as a strong candidate for natural selection. One variant of the EPAS1 gene differed between Tibetans and Han Chinese by 78% (87 vs. 9%). The authors also raised the possibility that the Tibetan and Han Chinese populations had diverged less than 3,000 years ago. If this were true, it would probably be the most rapid example of Darwinian evolution in humans. However, this assertion of the rapidity of the change has been challenged by other investigators, including Aldenderfer (22).

Research on this topic is moving at a fast pace, and the above account will soon be superseded. However, this new area is one of the most exciting recent developments in the area of high-altitude medicine.

Genetics and High-Altitude Diseases

There is much interest in whether genetic factors play a role in the prevalence of various high-altitude diseases, but research is at an early stage. Interested readers should consult one of the reviews, for example that by MacInnis and colleagues (23), which includes a table four pages long listing candidate genes and their possible links to high-altitude diseases.

Evidence for a link between genetics and high-altitude diseases is that several familial patterns of susceptibility have been described. This is particularly the case for high-altitude pulmonary edema, although no definitive gene differences have been identified (23). In addition, population patterns suggest a genetic basis. For example, Han Chinese have a much higher incidence of chronic mountain sickness than Tibetans at high altitude.

Phenotype Differences between Tibetans and Andeans

The two major groups of highlanders who have adapted well to high altitude, the Tibetans and Andeans, have different physical characteristics. The extent to which this is caused by genetic changes as opposed to other factors is unknown. Resting ventilation is lower in Aymara Andeans compared with Tibetans (8). The differences in resting ventilation are also consistent with the lower arterial oxygen saturations seen in Andeans, although there is considerable overlap. Thus, resting ventilation, hypoxic ventilatory response, oxygen saturation, and hemoglobin concentration are different between the two groups. Beall (8) has performed a sophisticated statistical analysis of the data and has shown that, in spite of the considerable overlap, the differences are real.

HIGH-ALTITUDE DISEASES OF LOWLANDERS

For additional information and detailed recommendations on therapy, see Reference 24.

Acute Mountain Sickness

Many people who ascend rapidly to high altitude develop acute mountain sickness (AMS). For example, 85% of tourists flying into the airstrip at Shayanboche (3,740 m) in Nepal had symptoms

(25). Common symptoms include headache, anorexia, nausea, malaise, lack of energy, disturbed sleep, and occasionally vomiting. Often the symptoms occur late on the day of arrival and are worst on the following 2 days. The condition is usually self-limiting, and after 2 or 3 days the symptoms disappear.

Rate of ascent is an important factor determining the incidence of AMS. The incidence of the disease in trekkers in Nepal who ascend to 3,800 m over 10 days is much smaller than for those who fly in. Fitness at sea level does not confer protection. There are anecdotal reports of people who are superb athletes at sea level but are severely affected at altitudes over 3,500 m. Individuals who develop AMS on one ascent are more likely to develop the disease on subsequent ascents. Gender has little effect, although some reports suggest that women are more at risk (26). Young people in their teens and early twenties seem to be more prone than older people (27, 28), possibly because they tend to be more active. In general, physiological measurements have not proved useful in predicting the incidence of AMS, although some studies have shown that a low hypoxic ventilatory response is a risk factor (29), whereas others disagree (30). Consistent with this, some other studies have shown a correlation between a low arterial oxygen saturation and the incidence of AMS (31, 32). Vigorous exercise apparently increases the risk (33), and often people are advised to avoid strenuous exercise on arrival at high altitude.

The pathogenesis of AMS is still debated, but there is some evidence that it is caused by increased intracranial pressure (34), although not all studies agree (35). One theory is that the raised central nervous system pressure is due to an increase in cerebral blood flow. A low arterial P_{O_2} causes cerebral vasodilatation, although the reduced arterial P_{CO_2} that accompanies the hyperventilation has the opposite effect. Another possible pathogenic factor is increased microvascular permeability. For example, all subjects taken abruptly to an altitude of 4,350 m on Mont Blanc developed symptoms of AMS, and all had increased plasma levels of six eicosanoids, which are known to affect vascular permeability (36). Whether hypoxia *per se* increases microvascular permeability has been debated over the years, but the general consensus is that there is no significant effect. Another possibility is that AMS is caused in part by an abnormal sodium and water balance. For example, one study showed that trekkers with AMS gained weight, whereas those without AMS had lost weight by the time they reached 4,243 m (37), although it may be that the AMS was the cause of the weight gain.

In the prophylaxis of AMS, by far the most important strategy is a slow rate of ascent. Various rules of thumb have been suggested. One is that above an altitude of 3,000 m, ascent should be limited to 300 m each day with a rest day at the same altitude every 2 or 3 days. However, there is considerable individual variability in the risk of AMS. Some trekkers can ascend as much as 500 m per day with no problem, whereas others are limited to 100 to 200 m per day to remain free of symptoms.

The most important medication for prophylaxis of AMS is acetazolamide. This can be started on the day of the ascent or 1 day before. Many controlled trials have demonstrated its efficacy. A few years ago, doses as high as 750 mg/d were recommended, but many people find that 500 or 250 mg per day is sufficient (38). Sometimes 125 mg taken at bedtime improves sleep and may improve symptoms of AMS. The side effects of acetazolamide include a mild diuresis and parasthesia in the hands and feet. These symptoms are usually not severe and are less at the lower doses. Carbonated beverages taste flat because of the effect of the carbonic anhydrase inhibition on taste receptors. The mechanism of action of acetazolamide is probably the mild metabolic acidosis caused by the inhibition of carbonic anhydrase. It therefore acts as a respiratory stimulant. There is a small chance of cross-reactivity in individuals with a history of sulfa allergy.

Dexamethasone is an effective drug at a dosage of 4 mg every 12 hours and is particularly useful for individuals with an allergy or intolerance to acetazolamide. Other drugs that have been used include aspirin and ibuprofen (39).

For the treatment of AMS, by far the best strategy is descent. Oxygen should be given if available. However, because the disease is usually self-limiting, many people remain at an altitude for 2 or 3 days to see if this is sufficient. If descent is impossible, acetaminophen or nonsteroidal antiinflammatory drugs can relieve the symptoms of AMS. If these conservative measures are insufficient, acetazolamide (250 mg every 12 h) or dexamethasone (4 mg every 6 h) can be added. However, every attempt should be made to descend.

High-Altitude Pulmonary Edema

Unlike AMS, high-altitude pulmonary edema (HAPE) is a potentially lethal form of high-altitude disease. It is most often seen in people who ascend rapidly. A typical presentation is someone who has been at high altitude for 1 or 2 days and develops the symptoms of AMS, although this is not always the case. Over the course of a few hours, the patient becomes increasingly breathless. Frequently this is more noticeable at night when the patient is lying down. A cough develops, and initially this is dry, but as it progresses it produces frothy white sputum. In severe cases, this becomes pink because of the presence of blood. On examination, rales (crackles) are heard particularly at the lung bases. Cyanosis may develop, and there is tachycardia and perhaps a mild pyrexia. Chest radiograph would show obvious changes of pulmonary edema. Patients who do not descend may rapidly deteriorate and die. The incidence of HAPE is not easy to determine, but an early report found an incidence of 0.57% in troops flown to an altitude of 3,500 m (40). Essentially the same incidence was reported in a series of adults going to La Oroya (altitude 3,750 m) (41). However, some studies have reported a considerably higher incidence, with as many as 10% of people who ascend rapidly to 4,500 m developing the condition (42). There is some suggestive evidence that subclinical pulmonary edema is common, and some trekkers diagnosed with AMS have crackles by auscultation and presumably have increased fluid in their lungs.

The pathogenesis of HAPE was a puzzle for many years. Initially left ventricular failure was suspected, but this was disproved when cardiac catheterization showed normal pulmonary artery wedge pressures. On the other hand, several studies have shown markedly elevated pulmonary artery pressures in this condition (43, 44). It was also shown that susceptible individuals have an unusually marked hypoxic pulmonary vasoconstriction (45), and they tend to have unusually high pulmonary artery pressures before the onset of HAPE (46). Exercise at high altitude is a risk factor (47), and patients with a restricted pulmonary vascular bed, for example caused by unilateral absence of a pulmonary artery, have been shown to be particularly at risk (48).

A breakthrough was the demonstration that the alveolar edema is of the high-permeability type with a large concentration of high-molecular-weight proteins (49, 50). It is believed that the hypoxic pulmonary vasoconstriction is uneven and that those capillaries that are not protected from the high pulmonary artery pressure develop mechanical failure of the extremely thin blood–gas barrier (Figure 3). Studies of animal lungs in which the capillary pressure was raised and the structure of the capillary walls examined by electron microscopy show clear evidence of ultrastructural changes (51). This is known as stress failure (52). An interesting feature of this stress failure in animal preparations is that if the pressure in the pulmonary capillaries is

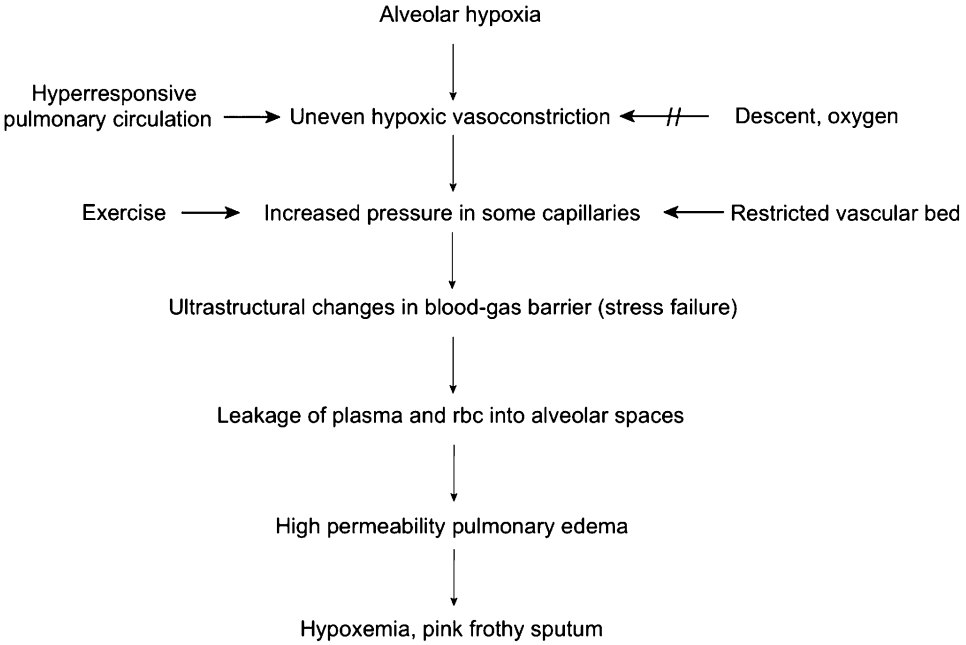

Figure 3. Diagram showing the pathogenesis of high-altitude pulmonary edema. rbc = red blood cells.

increased and then lowered to normal levels for a few minutes, a large number of the ultrastructural changes disappear. This rapid resolution is consistent with the rapid improvement in a patient's clinical status when he is moved to a lower altitude.

The cardinal feature of the treatment of HAPE is descent as quickly as possible. This often results in a remarkably rapid improvement. Oxygen should be administered if possible. If the patient cannot easily be moved, removal by helicopter is often indicated. If evacuation cannot be arranged and a Gamow or Certec bag is available, this may tide the patient over. (This is a bag into which the patient is placed, and the pressure is increased by pumping air into it.) The vasodilator nifedipene has been shown to be useful with a dose of 20 mg of the slow-release preparation by mouth every 12 h (53). Phosphodiesterase inhibitors may be useful but have not been systematically studied. Diuretics are contraindicated. Patients who have had HAPE are more likely to develop it again on ascent, and they should therefore ascend slowly. Nifedipene (20 mg of the slow-release preparation every 8 h) reduces the incidence of the disease (54).

High-Altitude Cerebral Edema

High-altitude cerebral edema (HACE) is uncommon but potentially lethal (55). It often begins as a severe form of acute mountain sickness; the pathogenesis of the two may be the same, with HACE being the extreme end of the spectrum. A common presentation is that the patient develops headache and malaise, and these progress to ataxia, confusion, altered consciousness, coma, and sometimes death. On examination there is papilledema, extensor plantar responses, and occasional focal neurologic signs affecting cranial nerves. The pathogenesis is almost certainly cerebral edema, possibly related to an increased cerebral blood flow. Autopsies have revealed cerebral edema with swollen flattened gyri (34, 56). Some MRI studies have shown abnormal T2 signals in white matter, particularly in the splenium and corpus callosum, consistent with edema (57). The incidence of HACE is difficult to determine, but it is less than that of HAPE.

Rapid descent is critical for treatment. Oxygen should be administered if available. Dexamethasone 4 to 8 mg initially followed by 4 mg every 6 hours should be given, and a portable compression bag should be used if available. Patients often respond rapidly when taken to a lower altitude.

HIGH-ALTITUDE DISEASES OF HIGHLANDERS

Chronic Mountain Sickness

Residents of high altitudes sometimes develop a disease characterized by severe polycythemia and an array of neurologic symptoms including headache, fatigue, somnolence, and depression. Hematocrit levels as high as 80% have been recorded (58). The very high hematocrit increases the viscosity of the blood, and sometimes it is difficult to remove a venous blood sample.

The pathogenesis of CMS is poorly understood. Possible factors include a low hypoxic ventilatory response, sleep-disordered breathing, increasing age, genetic factors, and possibly exposure to heavy metals such as cobalt. Tibetans have a lower incidence of CMS than Andeans, consistent with their lower hematocrit. The management of these patients is difficult. Acetazolamide at a dosage of 250 mg daily has been shown to provide some benefit (59). Venesection improves the patient but needs to be repeated frequently. The only cure is descent to a lower altitude, but this is impossible for many of these patients.

High-Altitude Pulmonary Hypertension

High-altitude pulmonary hypertension takes two forms. In adults it has been seen in Indian soldiers who have been posted to altitudes of 5,800 to 7,000 m for several months (60). The patients presented with dyspnea, cough, and angina of effort, and on examination there was dependent edema. On investigation at lower altitudes, there was pulmonary hypertension and right ventricular enlargement. The pathogenesis seems to be right ventricular failure following prolonged hypoxic pulmonary vasoconstriction. The condition has also been described in Tibet (61). Cattle taken to high altitude in Colorado develop a similar condition known as brisket disease (62). Treatment is by descent.

Infants born at high altitude may develop a form of high-altitude pulmonary hypertension. This most frequently occurs in Han Chinese (63, 64) and is consistent with the well known fact that Han Chinese do not tolerate high altitude as well as Tibetans.

MITIGATION OF HIGH-ALTITUDE HYPOXIA BY OXYGEN ENRICHMENT OF ROOM AIR OR INCREASING THE BAROMETRIC PRESSURE

There are two general strategies for dealing with medical problems of high altitude. One is to accept the low inspired P_{O_2} and attempt to reduce the consequences by acclimatization or treating the disease. The other is a proactive, where the inspired P_{O_2} is increased by raising the oxygen concentration of the air, by increasing the barometric pressure, or by a combination of both.

Oxygen Enrichment of Room Air

The details of oxygen enrichment of room air were first worked out approximately 20 years ago (65), and the first full-scale use was in a radiotelescope installation in northern Chile at an altitude of 5,000 m (66). The principle is simple. Oxygen is generated from air using a commercial oxygen concentrator into which air is pumped at high pressure through a synthetic zeolite, which adsorbs the nitrogen so that the effluent gas has an oxygen concentration of 90 to 95%. After 20 to 30 s, the zeolite is unable to adsorb more nitrogen, and the compressed air is moved to a second cylinder containing the same material. The first cylinder is then purged by blowing air through it at normal pressure, and the cycle is repeated. The result is a continuous production of 90 to 95% oxygen.

Initially it was thought that an oxygen-enriched room would need to be gas tight, but in fact the oxygen is simply added to the air conditioning and gas leaves the room through various random leaks. In some installations, a double door is used to reduce the loss of the oxygen-enriched air when people enter or leave. An issue that is often raised is whether oxygen enrichment of this kind causes a fire hazard. The first point to emphasize is that the P_{O_2} in the oxygen-enriched room air at high altitude is always far below the P_{O_2} at sea level. The National Fire Protection Association has analyzed this issue in detail, and tables are available showing the highest safe oxygen enrichment level at any altitude (67).

The reason why oxygen enrichment of room air is so powerful is that a small degree of added oxygen results in a large reduction in equivalent altitude (Figure 4). The term "equivalent altitude" refers to the altitude at which the moist inspired P_{O_2} when the subject is breathing ambient air is the same as the inspired P_{O_2} in the oxygen-enriched environment. For most altitudes, 1% of oxygen enrichment results in a reduction of equivalent altitude by about 300 m. In other words, at the 5000-m site in northern Chile, increasing the oxygen concentration in the room from 21 to 27% reduces the equivalent altitude by 1,800 m. Therefore, we effectively go from an altitude of 5,000 m to 3,200 m, which is much more easily tolerated. Oxygen enrichment of room air is being used in many facilities throughout the world. One of the most impressive facilities is the Atacama Large Millimeter Array radiotelescope in northern Chile at an altitude of 5,050 m. This is an enormous multinational, multimillion-dollar facility.

One of the most remarkable examples of oxygen enrichment of room air is the Chinese train that runs between Golmud in Qinghai Province to Lhasa, the capital of Tibet. The altitude of the track is above 4,000 m for most of the time and exceeds 5,000 m at one point. These very high altitudes represent a major risk to passengers. The solution has been to install oxygen generators in every passenger car. The result is that the oxygen concentration is raised to as high as 25% when the train is passing through the highest altitudes. Each passenger car has a panel that allows the passengers to read the oxygen concentration provided by the generator and the oxygen concentration in the air of the passenger car. To oxygenate a single room or a suite of rooms is one thing, but to oxygenate a whole train is much more ambitious. The Chinese engineers are to be congratulated on this feat.

Oxygen enrichment of high-altitude telescope facilities and the Chinese train are major engineering projects. However, oxygen enrichment of room air has potential value on a much smaller scale, for example in the bedrooms of houses in ski resorts (68). An analysis shows that all resorts up to an altitude of 3,250 m (10,600 ft) can have the equivalent altitude reduced to 1,000 m (3,280 ft) by oxygen enrichment without incurring

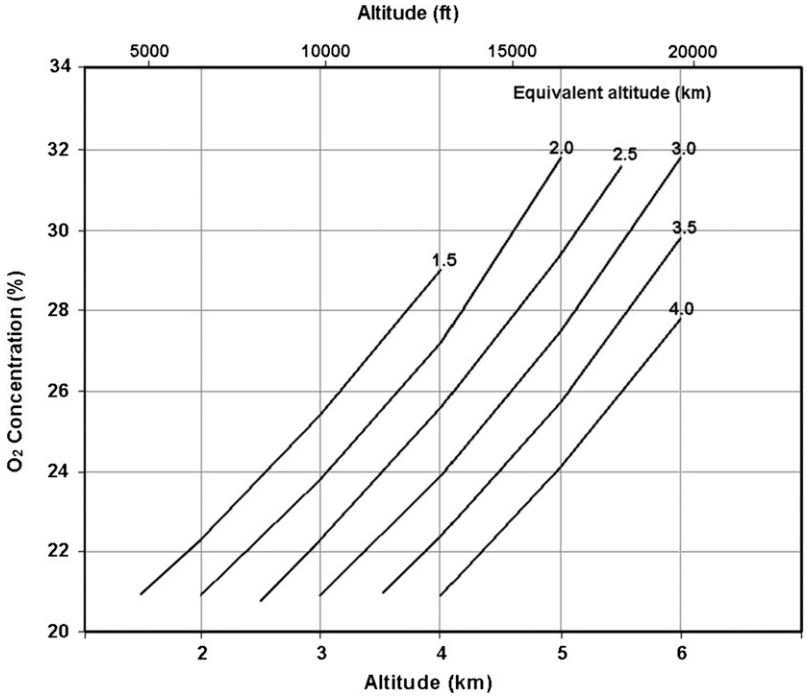

Figure 4. Plot showing the effectiveness of oxygen enrichment of room air. The oxygen concentrations required to reduce the equivalent altitude to 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 km are shown. For example, suppose we are at an altitude of 5,000 m and wish to reduce the equivalent altitude to 3,000 m. The graph shows that the oxygen concentration required is about 27.5%. All the oxygen concentrations on the lines are below the values that incur a fire hazard.

a fire hazard. Many people who travel to altitudes of about 2,500 m (8,200 ft), where ski resorts such as Aspen and Vail in Colorado are located, have serious difficulties with sleeping for the first two or three nights, and oxygen enrichment of the room air provides considerable improvement. Measurements of sleep architecture during oxygen enrichment have been made at an altitude of 3,800 m, and these studies have shown considerable improvement in sleep, with fewer apneas and less time spent in periodic breathing with apneas (69).

Increased Barometric Pressure

The second way of mitigating the problems of high-altitude hypoxia is to raise the barometric pressure. This is the procedure used in passenger aircraft. The first use of pressurized cabins took place in about 1939, and now millions of passengers every year benefit from this procedure. Typically the aircraft cabin altitude is not allowed to exceed 8,000 ft (2,440 m), and many aircraft now have a lower cabin altitude of 6,000 ft (1,830 m). Some newer aircraft have a cabin altitude as low as 5,000 ft (1,500 m). Of course an aircraft has an advantage over a train in that no passengers leave the aircraft between take-off and landing, whereas a train may stop at various stations. Lowering the cabin pressure is advantageous for the passengers but is associated with the penalty of a heavier aircraft to withstand the pressure difference between the cabin and the outside air and the resulting higher fuel consumption.

Hybrid System

A third way to mitigate the hypoxia of high altitude is to use a combination of increased pressure and increased oxygen concentration. This has apparently never been used but is an interesting prospect. For example, rather than increase the weight and therefore fuel consumption of an aircraft, by reducing the cabin altitude from 8,000 to 5,000 ft, the same reduction in equivalent altitude could be obtained by raising the oxygen concentration in the cabin from 21 to 24%. Onboard oxygen generators are commonly used, mainly to provide nitrogen to purge the air in fuel tanks and thus reduce the risk of an explosion caused by a spark. Onboard oxygen generators produce oxygen, and therefore the possibility of raising the oxygen concentration in the cabin seems feasible.

COMMERCIAL AND MILITARY ACTIVITIES AT HIGH ALTITUDE

Mining

Mining activities at high altitude have a long history, for example in the Andes before the Spanish conquest. Recently there has been a great increase in high-altitude mining partly because commodities such as copper continue to be in great demand and because many of the ore deposits at moderate altitudes are becoming exhausted. Many of the new mines are in the Andes, but increasingly mineral deposits at high altitude are being mined in Tibet.

High-altitude mines fall into two categories. Many of the old mines, such as that at Cerro de Pasco, Peru (altitude 4,300 m), have complete communities at the altitude of the mine. The families are located there, and children grow up at high altitude. The wisdom of this has been debated because there is some evidence that children grow more slowly at high altitude, although nutrition may be another factor (70). Another feature of these old mining towns is that they need to provide a large infrastructure, including schools, medical facilities, etc., which increases the expenses of the mine.

Partly as a result of this, the modern tendency is not to have the families at the mine but to use a commuting pattern in which the miners ascend to the mine for a period and then return to their families. A good example of this is the Collahuasi mine in northern Chile, where the working areas of the mine are at an altitude of 4,400 to 4,600 m and the miners sleep at the lower altitude of 3,800 m. Several thousand people work at the mine, which is one of the largest copper mines in the world. However, the miners' families live in Iquique on the coast, and the miners are bused up to the mine at the beginning of the week. Typically they spend 7 days at the mine, where they work up to 12 hours per day. At the end of 7 days they are bused down to Iquique, where they spend the next 7 days with their families, and the cycle is repeated.

A number of studies have been performed on these miners over a period of 31 months (71). Hematocrit increased over the first 12 to 19 months, although it had returned to its sea level value at the end of 31 months. Mean systemic arterial pressure was increased at high altitude, but systolic pulmonary artery pressure measured by echocardiography did not change significantly over 19 months. Maximal exercise at sea level decreased by about 12% over the 31-month period. The miners continued to have some symptoms of AMS on the first or second day of ascent to altitude. Other schedules for the commuting pattern have been tried, but the 7-by-7-day schedule described here is probably the most common.

Another extraordinary mine still in the development stage is at Toromocho about 140 km east of Lima, Peru. The ore deposits are at an altitude of 4,700 to 4,900 m, and a challenging problem is that much of this is under the existing town of Morococha, which will have to be moved. The proposed camp with dormitories will be at 5,000 m, where the proposal includes 11 three-story dormitories holding up to 5,000 people. This altitude may not be a problem for highlanders, such as those from Morococha who are used to living at over 4,000 m; however it will provide a severe hypoxic stress to lowlanders, especially during sleep. One proposal is to use nasal catheters to provide oxygen enrichment during the night, but this has not been attempted on such a large scale. Ideally oxygen enrichment of room air for the dormitories could be installed, but this would be a very expensive undertaking for such a large number of people. Modern mining requires highly skilled people to handle the enormous mechanical shovels and trucks in these open-cut mines, and it seems unlikely that there will be enough highlanders with the necessary skills, so many people will need to come from lower altitudes.

Military Operations

The dispute between India and Pakistan over the Jammu-Kashmir region has resulted in an unprecedented number of young people being exposed to extreme altitude for long periods of time. Large numbers of soldiers have been stationed at altitudes of up to 7,000 m for many months. Many of these people come from altitudes near sea level, such as the plains of India. An account of some of the problems has been published (72). This situation has been responsible for the appearance of the new medical condition of high-altitude pulmonary hypertension in adults. The young men develop right heart failure with peripheral edema just as do the cattle at high altitude that develop brisket disease. Other medical problems are seen in this condition. For example, there is an increased incidence of stroke in these young men (73). A feature of this population is that it is difficult to evacuate them to lower altitudes rapidly. Occasionally this can be done by helicopter, but this option is not available for large numbers of people. This situation is in contrast to high-altitude mines in the Andes, where patients can be bused down to near sea level within a few hours.

Author disclosures are available with the text of this article at www.atsjournals.org.

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