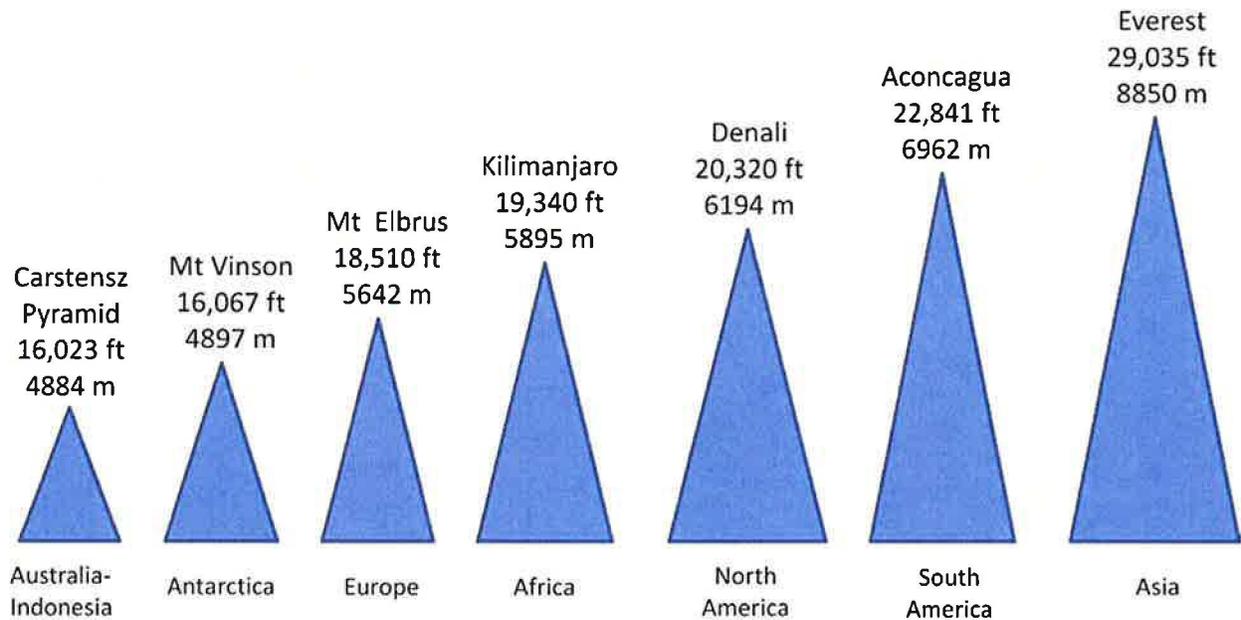


Physiology and Pathophysiology with Ascent to Altitude: Lessons Learned from the Seven Summits

By

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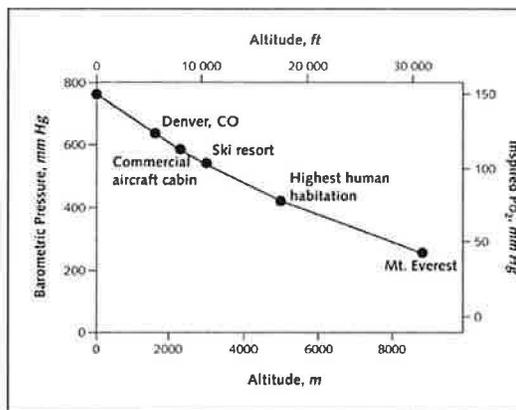
Introduction

Ascending to high altitude is accompanied by a series of physiologic changes elicited by a fall in the partial pressure of oxygen. These changes help to maintain oxygen delivery to tissues relatively well preserved despite the hypoxic environment. The process by which an individual adapts to altitude is known as acclimatization. The success of the acclimatization process shows a large degree of individual variability. At a given altitude one individual may thrive quite readily whereas another may develop a life threatening complication. While a number of factors are known to increase the risk of altitude related illness in many instances no underlying predisposition can be identified. Since greater than thirty million people visit high altitude regions annually it is important for physicians to be familiar with the physiologic changes that accompany travel to altitude and be aware of strategies available to both prevent and treat altitude specific illness (1).

Barometric Pressure, Hypoxia, and Altitude

Barometric pressure is a measure of the downward force exerted by the atmosphere at a given point. This force is greatest at sea level since the mass of air above this point is at its greatest. At progressively higher altitudes the barometric pressure falls since the atmospheric mass above the measurement point becomes smaller. A consequence of this decrease in pressure is less compression of the surrounding air and thus a decrease in air density or, stated differently, the air becomes thinner with altitude.

Relationship Between Altitude, Barometric Pressure and Inspired PO_2



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to consider the decrease in air density that accompanies the fall in barometric pressure. In a given volume of air there will be a decrease in the total number of molecules. The percentage of the existing molecules made up of oxygen remains the same, however, the absolute number of oxygen molecules has decreased.

One additional factor worth considering is the effect of solar radiation to cause upwelling of the atmosphere at the equator. This results in the column of air being higher at locations closer to the equator such that a given altitude near the equator will have a higher barometric pressure as compared to the same altitude closer to one of the poles. In terms of barometric

At sea level the fraction of inspired oxygen is 0.21. This value remains the same with increases in altitude. In other words the percentage of oxygen in the atmosphere is the same at 30,000 feet as it is at sea level. What changes is the barometric pressure. The fall in barometric pressure leads to a decline in the partial pressure of oxygen. Since the transfer of oxygen from the alveolar space to the pulmonary capillary is in part determined by the partial pressure gradient, this decline will lead to impaired oxygenation. Another way to view these changes is

pressure the summit of Denali at 20,320 feet is far enough north to be the rough equivalent of 23,000 feet on Mt Everest.

Physiologic Changes with Acclimatization

Under normal circumstances there is a fall in the partial pressure of oxygen as it is transported from the air through the lungs and ultimately to the tissues. This decline in partial pressure is known as the oxygen cascade. Since the starting point of the cascade is reduced with altitude, oxygen delivery to the tissues can be significantly reduced. The process of acclimatization serves to minimize any decrease in tissue oxygen delivery so that human performance is maintained near that of sea level. The physiologic responses that comprise the acclimatization process primarily affect the two determinants of tissue oxygen delivery, namely, arterial oxygen content and to a lesser extent cardiac output. Oxygen delivery can be calculated as:

$$\text{Oxygen Delivery (Do}_2\text{)} = \text{Cardiac output (Q)} \times \text{Arterial Oxygen Content (CaO}_2\text{)}$$

$$\text{Oxygen Delivery (Do}_2\text{)} = (\text{Heart rate} \times \text{stroke volume}) \times [([\text{Hg}] \times \text{SaO}_2 \times \text{H}) + (\text{PaO}_2 \times \text{S})]$$

where [Hg] is hemoglobin concentration, SaO₂ is arterial oxygen saturation of hemoglobin, H is Hufners constant, PaO₂ is arterial partial pressure of oxygen, and S is the solubility coefficient of oxygen.

The arterial oxygen content (CaO₂) reflects the total number of oxygen molecules in arterial blood both bound and unbound to hemoglobin. The greatest contributor to the maintenance of CaO₂ during acclimatization is the involuntary increase in ventilation (1). A drop in the Po₂ of the arterial blood leads to hypoxic stimulation of peripheral chemoreceptors primarily in the carotid and aortic bodies causing an increase in the depth and rate of breathing. This effect is known as the hypoxic ventilatory response. Increased ventilation lowers the alveolar Pco₂ and increases the alveolar Po₂ since the two are inversely related for a fixed rate of CO₂ production according to the alveolar gas equation:

$$\text{PAO}_2 = \text{PIo}_2 - (\text{PAco}_2/\text{R})$$

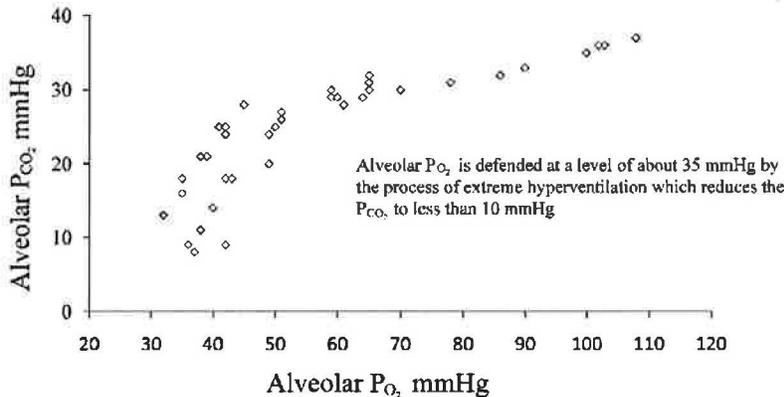
where PAO₂ is the partial pressure of O₂ in the alveoli, PIo₂ is the fraction of inspired oxygen, PAco₂ is the partial pressure of CO₂ in the alveoli, and R is the respiratory exchange ratio. A vigorous hypoxic ventilatory response limits the fall in alveolar Po₂ in the setting of decreased inspired Po₂ thereby maintaining a steep gradient for diffusion of oxygen from the alveoli to the blood in the pulmonary capillaries.

A reduction in PAco₂ and therefore arterial Pco₂ leads to respiratory alkalosis which at sea level would normally exert an inhibitory effect on respiration causing arterial Pco₂ and pH to return to normal levels. However, at altitude this inhibitory effect is overridden by central medullary chemoreceptors such that high levels of ventilation are maintained. The persistent increase in ventilation is due to the exit of HCO₃ from the cerebrospinal fluid with subsequent lowering of pH which in turn stimulates ventilation. Acidification of the cerebrospinal fluid is linked to decreased HCO₃ reabsorption in the proximal tubule of the kidney which is a

compensatory response to chronic respiratory alkalosis. This renal response becomes fully manifest over the course of two to three days. In addition to the acid-base changes increased ventilation is also driven by a sensitization of the carotid body to hypoxia during prolonged exposure to high altitude.

The hypoxic ventilatory response not only increases P_{aO_2} but also contributes to an even greater increase in SaO_2 . At extreme altitude the P_{aO_2} lies on the steep slope of the oxygen-

Alveolar P_{O_2} and P_{CO_2} of Acclimatized Humans at High Altitude



disassociation curve such that the affinity of hemoglobin of oxygen is greatly increased. As a result, for any increase in P_{aO_2} , the increase in oxygen saturation will be proportionately greater.

The magnitude of the hypoxic ventilator response can be enormous. At the summit of Mt. Everest alveolar ventilation is increased approximately five-fold such that the P_{CO_2} is reduced to 7-8 mmHg (2). This extreme degree of ventilation limits the fall in PA_{O_2} to around 35

mmHg even though the inspired P_{O_2} is only 29% of its sea level value. At any given altitude there is individual variability in the extent of the hypoxic ventilatory response. As discussed below, a less vigorous response is associated with decreased performance as well as a higher risk for altitude related illness (3).

Changes in hemoglobin concentration as well as its affinity for oxygen also contribute to maintenance of arterial oxygen content (CaO_2) with sojourns to altitude. Within the first one to two days of arrival to altitude there is a rapid rise in hemoglobin concentration due to the hemoconcentrating effect of a fall in plasma volume (4-7). This decrease in plasma volume ranges from 15 to 25% and roughly correlates with the degree of altitude attained. Circulating levels of erythropoietin also increase rapidly with peak levels occurring 48-72 hours after arrival to a new altitude. This rise is short lived however as levels tend to return toward baseline values over the subsequent 5-10 days (5,8). Red cell mass begins to slowly increase shortly after the rise in erythropoietin levels but takes several weeks to become fully manifest (9,10). For subjects who remain at a given altitude for periods of less than a week, the change in red cell mass is trivial and would not make a significant contribution to the acclimatization process.

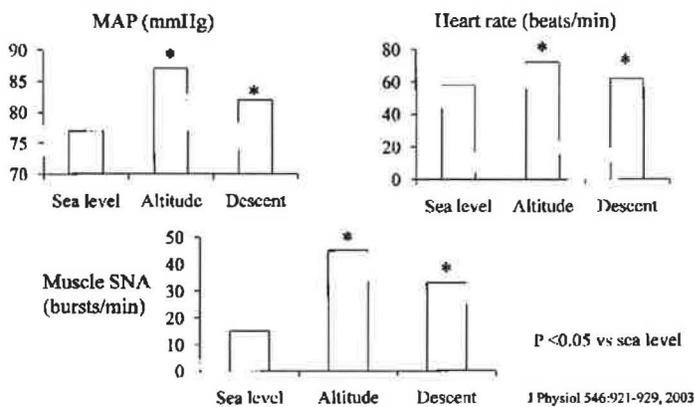
In addition to increases in hemoglobin concentration, the acclimatization process leads to changes in factors that can shift the position of the oxygen disassociation curve in such a way so as to either increase or decrease oxygen affinity. The P_{aO_2} at which hemoglobin is 50% saturated is called the P_{50} . Increased blood pH shifts the curve leftward reflecting increased affinity of hemoglobin for oxygen whereas accumulation of red cell 2,3-diphosphoglycerate (2,3-DPG) shifts the curve rightward reflecting decreased affinity for oxygen (11). The American

Medical Research Expedition to Everest (AMREE, 1981) studied the red cell response and oxygen disassociation curve in climbers at various camps in route to the summit of Mt Everest (12). With increasing altitude the investigators found red cell 2-3-DPG increased but the predicted rightward shift was counterbalanced by an increase in blood pH such that the P_{50} remained relatively unchanged up to an altitude of 6300 m. Beyond this altitude the curve progressively shifted leftward and the P_{50} decreased (from 28.1 Torr at sea level to 19.4 Torr at 8848 m) due to the stronger effect of the high blood pH. This reduction in P_{50} further contributes to the maintenance of arterial O_2 saturation and arterial O_2 content at extreme altitude.

Altitude also affects cardiac output which is the other determinant of oxygen delivery. Within 24 hours after arrival to altitude cardiac output and heart rate are increased (13). These changes are thought to be due to hypoxia induced increases in sympathetic nerve activity. Interestingly this increase in sympathetic nerve activity remains persistent even in well acclimatized subjects. Using peroneal microneurography sympathetic nerve discharge remains elevated in subjects after four weeks at an altitude of 5260 meters as compared to values obtained at sea level (14). Administration of oxygen in order to eliminate chemoreflex activation

SNA Associated with ↑ HR and MAP

8 subjects studied at 4 wks at 5260 m in Bolivian Andes and after descent



or saline to reduced baroreflex deactivation has only a minor effect in reducing sympathetic activity leaving the underlying mechanism of the chronic overactivity unexplained.

Despite the increase in sympathetic nerve activity heart rate and cardiac output tend to fall over several days after arrival to a new elevation (13,15). The decline in heart rate is of a variable degree and has been attributed to increased vagal input as well as down regulation in the number of β -adrenergic receptors. Cardiac output falls, in part, due to

the decline in heart rate but also as a result of a decline in stroke volume (16). The decrease in stroke volume is primarily due to a reduction in preload resulting from the fall in plasma volume which typically accompanies the acclimatization process.

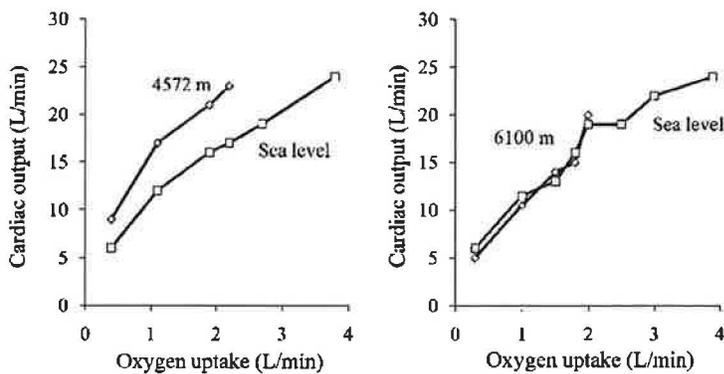
Stroke volume may also decrease as a secondary effect of hypoxic vasoconstriction of the pulmonary vasculature. At an altitude of approximately 3000 m pulmonary artery pressure begins to increase. The increase in pulmonary vascular resistance will cause right ventricular pressure to increase and potentially cause leftward deviation of the cardiac septum. This deviation can encroach upon the left ventricular outflow tract and compromise its function contributing to a fall in stroke volume and cardiac output. This effect is supported by studies examining altitude-induced changes in pulmonary artery pressure and cardiac output after the administration of sildenafil (17,18).

Sildenafil is a phosphodiesterase-5 enzyme inhibitor which prevents the degradation of the vasodilator cGMP. With use of echocardiographic techniques, administration of oral sildenafil has been shown to normalize the increase in systolic pulmonary artery pressure in

subjects who travel from sea level to 4350 m (17). The drug also increases cardiac output during exercise in subjects at simulated altitude of a comparable degree. By contrast there is no effect on cardiac output during exercise at sea level when pulmonary artery pressures are presumably normal (18). While indirect, these studies are at least consistent with the notion that relief of hypoxic pulmonary vasoconstriction and lowering of right ventricular pressure allows left ventricular stroke volume to be maintained by preventing septal encroachment into the left ventricle.

Despite the fall in cardiac output discussed above, the performance of the heart is well maintained even at extreme altitudes. Operation Everest II was a study in which normal subjects were placed in a decompression chamber at sea level and exposed to a progressive lowering of inspired O₂ pressure so as to simulate a 40 day ascent of Mt. Everest. In this study a variety of circulatory parameters were examined both at rest and with exercise at progressively higher simulated altitudes (19). With acute hypoxic exposure heart rate and cardiac output were found to be greater at altitude than at sea level at any submaximal level of exercise. With prolonged hypoxic exposure heart rate remained at slightly higher levels but cardiac output began to exactly match sea level values for any given work load. Cardiac output only exceeded sea level values at 43 Torr, the highest altitude obtained in the study. Mixed venous Po₂ progressively decreased

Relationship Between Cardiac Output and Oxygen Consumption with Acute and Chronic Exposure to Altitude



with the fall in barometric pressure indicating greater tissue extraction of O₂ as a mechanism to offset the decrease in arterial O₂ transport. These findings suggest that a given submaximal O₂ consumption is accomplished by lowering venous O₂ in preference to increasing cardiac output in the setting of altitude-induced decreases in arterial O₂ content. At some point tissue O₂ extraction is maximal and venous O₂ can no longer be further reduced. At this point increases in cardiac output are required to offset the decrease

in arterial O₂ content. Despite the extreme conditions there is no electrocardiographic evidence of myocardial ischemia and cardiac contractility as assessed by ultrasound is well maintained.

Body Weight and Skeletal Muscle Changes with Altitude

Traditional thinking predicted the chronic hypoxia of altitude would lead to increased capillary density in tissues such as skeletal muscle. Initial studies examining this possibility showed capillary density was indeed increased. However, these studies failed to consider the relationship of capillary density to muscle fiber changes. When examined in this fashion the apparent increase in capillary density is found to be the result of a marked decrease in muscle fiber cross-sectional density (20,21). Similarly it was predicted aerobic mitochondrial enzymes

would be increased in order for cellular energy demands to be met at altitude. Once again this prediction proved to be incorrect.

Skeletal muscle biopsies taken from climbers on Mt Everest show a decrease in mitochondrial volume by up to 30% (22,23). The changes in mitochondrial volume are accompanied by significant decreases in the activity of enzymes responsible for aerobic oxidative metabolism. This negative effect on muscle fiber size and tissue oxidative capacity is similar to what has been reported in subjects exposed to simulated altitude in the Operation Everest II project. In contrast, proteins involved in the cellular transport of bicarbonate, protons, and lactate are increased in both skeletal muscle and red blood cells (24). Such changes may increase the buffer capacity of muscle and represent an adaptation to altitude allowing for increased exercise performance.

The histologic changes noted above parallel the significant declines in body weight and overall muscle mass which occur with chronic exposure to altitude. In the Operation Everest II project weight was reduced by 7.44 kg over the study period representing an 8.9% decline from the initial body weight (21,22). Total muscle area calculated in 6 subjects from CT scans of the thigh and upper arms showed decreases of 13 and 15% respectively. The reduction in weight and muscle mass found in the study can be more confidently attributed to hypobaric hypoxia since the participants were not subjected to cold, overexertion, and other rigors of climbing high mountains.

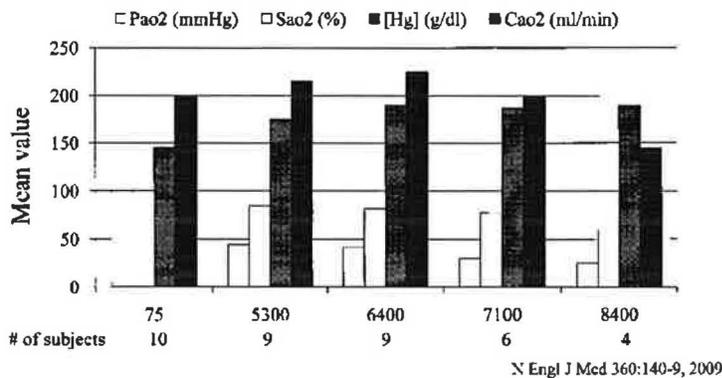
The Operation Everest III study examined the long term effect of hypobaric hypoxia on appetite using a hypobaric chamber and simulating the ascent of Mount Everest over a 31 day period (25). Weight was reduced by an average of 5 kilograms in the study participants. A reduction in appetite with reduced energy intake was the primary factor responsible for the reduction in body mass. During the course of the study subjects tended to eat more frequent

meals but meal size was reduced due to a more rapid increase in satiety. In those subjects who experienced acute mountain sickness interest in food was lost. Increased leptin levels have been implicated as a mechanism in the loss of appetite with altitude (26).

A still unanswered question is why maximal O₂ consumption and maximal exercise capacity remain substantially reduced after high altitude acclimatization despite the fact that arterial O₂ content increases to values that nearly match values at sea level (27,28). One explanation

for this finding is that the enhanced O₂ transport capacity is not proportionately delivered to those vascular beds with the highest O₂ demand. Exercising muscle is in competition with noncontracting tissues for the delivery of O₂. At altitudes up to 4000 m peak blood flow to the leg is similar to sea level values. After acclimatization at higher altitudes the partitioning of

Arterial Blood Gases and O₂ Content in Climbers of Everest



cardiac output becomes less directed to contracting muscle such that a greater proportion is directed to noncontracting tissues at maximal exercise. As a result the extra O₂ carrying capacity of blood gained with altitude cannot be fully exploited by exercising muscle and maximum oxygen uptake and exercise performance are reduced.

Adaptation to high altitude is likely to show a great deal of variability and may be influenced by factors that regulate the microcirculatory bed. Maximum O₂ consumption is

Oxygenation Measurements Upon Descent from Summit of Mt Everest (N=4) 8400 m

Variable	Group Mean
pH	7.53
Pao ₂ (mmHg)	24.6
Paco ₂ (mmHg)	13.3
HCO ₃ (mmol/l)	10.8
Lactate (mmol/l)	2.2
Sao ₂ (%)	54
Hg (g/dl)	19.3

increased in indigenous high altitude Tibetans and has been attributed to increased lung capacity and enhanced pulmonary gas exchange efficiency (29). Recent studies have implicated differences in the behavior of the microvascular to account for these differences. Forearm blood flow was measured and compared in a group of 88 Tibetans at 4200 m and 50 residents of the United States at 206 m (30). Forearm blood flow was found to be greater than double that measured in low-altitude residents.

Tissue oxygen delivery was also more than two times greater as a result of the increased flow as well as a higher hemoglobin concentration despite a lower arterial oxygen content. Circulating concentrations of bioactive nitric oxide products were 10 fold higher in comparison to sea level controls. These findings suggest important differences in regulation of blood flow in Tibetans who are adapted to high altitude hypoxia. It is interesting to speculate that such differences could lead to greater partitioning of blood flow with exercise to contracting muscles and therefore account for the greater exercise performance observed in high altitude natives.

High Altitude Illness

The physiologic changes that comprise the acclimatization process can be very effective in maintaining tissue oxygen delivery and enabling individuals to reach the greatest heights on earth (31,32). However in many instances these physiologic changes may be inadequate such that the sojourn to altitude and the attendant hypoxia is complicated by altitude-associated medical illness. The rate of ascent, the absolute change in altitude, and individual physiology are the primary determinants as to whether illness will develop or not. High altitude illness can be divided into three major conditions: acute mountain sickness, high altitude pulmonary edema, and high altitude cerebral edema.

Acute Mountain Sickness

Acute mountain sickness (AMS) commonly develops in those who arrive at altitudes greater than 3000 m from sea level but can occasionally develop at altitudes as low as 2000 m (33,34). The condition is characterized by headache, anorexia, nausea and sometimes vomiting, lightheadedness, insomnia, and fatigue. These symptoms usually begin within 12 hours of

arrival but then often subside over the ensuing 2-3 days assuming no further gain in altitude is attempted and exertion is avoided. Insomnia may persist for longer periods of time. Descent to a lower altitude leads to rapid resolution of the symptoms.

There is not a readily identifiable way to predict who will develop AMS prior to arrival at altitude. Men and women appear to be equally as susceptible and physical fitness is not protective against the illness. There is a suggestion that person over 50 years of age are less prone as compared to younger persons.

Individual variability in the physiologic response to hypoxia is the most likely factor in determining who develops AMS. A failure to adequately increase ventilation upon arrival to altitude is one such response implicated as a risk factor for development of AMS (35). The acute hypoxic ventilatory response to a simulated altitude of 4800 m was compared in 8 subjects with a history of AMS and 4 subjects with no symptoms during prior altitude exposure. At the simulated altitude, the 8 AMS subjects became symptomatic and had lower minute ventilations, lower arterial O₂ saturations, and higher end-tidal Pco₂'s in comparison to the asymptomatic subjects who remained well under the study conditions.

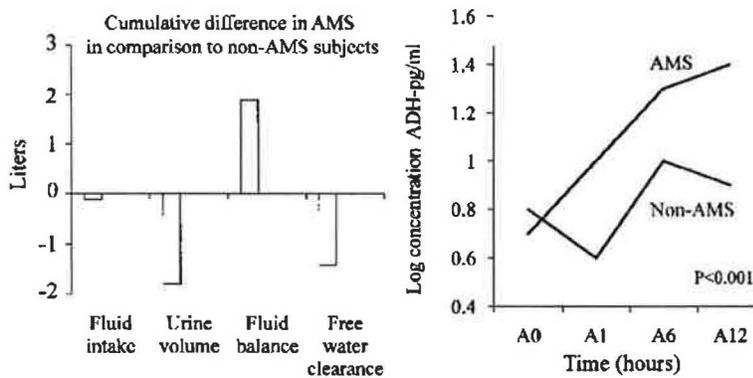
An association between relative hypoventilation and development of AMS was also found in a study of 42 healthy subjects first examined at Kathmandu Nepal (1337 m) and again after arrival in Pheriche Nepal (2750 m) 4-6 days later (36). The subjects who developed AMS were also noted to have an increase in body weight during the ascent as opposed to weight reduction which typically occurs as a result of the normal fall in plasma volume with ascent to higher altitude. Using a scoring system, a positive association was seen between severity of AMS symptoms and percent increase in body weight. By contrast a negative correlation was seen between change in body weight and degree of ventilation. The relative hypoventilation in those who gained weight was confirmed by higher values for Pco₂ and lower values for arterial O₂ saturation when compared to those who lost weight and remained well. The subjects who gained weight tended to have a higher urine osmolality and a trend towards a lower hematocrit.

An association between early fluid retention and symptoms of AMS has also been demonstrated using a decompression chamber to simulate conditions of altitude (37). A group of

51 normal subjects were subjected to repetitive 12 hour exposures to a simulated altitude of 4880 m (16000 feet). Using the Lake Louise scoring system a comparison was made between 16 subjects with the lowest AMS score and 16 others with the highest scores. As compared to those with a low score, urine flow in the first three hours of exposure and the plasma Na⁺ concentration at six hours were significantly reduced in the high score subjects. In addition, free water clearance was significantly reduced and plasma

Fluid Retention and AMS

Simulated altitude of 4880 m for 12 hours comparing
16 subjects with lowest AMS Scores and 16 with highest scores



J Appl Physiol 98:591-597, 2005

levels of ADH were significantly increased in the high score AMS group. In addition to the fluid retention, the high score group had significantly lower values for arterial O₂ saturation and Pao₂. These studies are consistent with the concept that diuresis and loss of body weight are normal and favorable responses to acute high altitude exposure while fluid retention and weight gain are adverse responses and are associated with an inadequate ventilatory response.

The pathogenesis of AMS is not known with certainty. Hypoxia-induced cerebral vasodilation is likely to play an important role (1). Hypoxia may also alter the permeability of the blood brain barrier so as to predispose to a vasogenic form of cerebral edema. The inadequate ventilatory response (causing a more severe degree of hypoxia) and fluid retention (causing volume expansion) observed in those who develop AMS would be expected to exacerbate both increased flow and pressures in the brain. A higher cerebrospinal fluid to brain volume might be protective against AMS since displacement of CSF could serve as an initial defense against a rise in cerebral pressure for any degree of cerebral edema (38). This mechanism may account for the decreased risk of AMS in persons over 50 years of age since the ratio of CSF to brain volume is likely to be greater as a result of age-related cerebral atrophy.

Prevention of AMS is best accomplished by a gradual ascent allowing adequate time for acclimatization. A useful rule of thumb is to limit each day's ascent to no more than 300-400 m after reaching an altitude of 2500 m. Adding an extra rest day for every increase of 600-1200 m at this altitude will further decrease the likelihood for development of AMS. Pharmacologic prophylaxis is recommended when one ascends rapidly from sea level to a sleeping altitude of 3000 m as might occur when arriving to a high altitude city by air or if there is a prior history of AMS.

Acetazolamide administered at a dose of 125 to 250 mg twice daily is an effective therapy for the prevention of AMS (39,40). The drug inhibits the enzyme carbonic anhydrase in the proximal nephron causing decreased bicarbonate reabsorption and subsequent generation of a metabolic acidosis. Metabolic acidosis is thought to attenuate the inhibitory effect of hypoxia-induced respiratory alkalosis on central chemoreceptors such that ventilation is increased (41). Direct effects on peripheral chemoreceptors and diuresis may also play a role in the beneficial effects of the drug.

Acetazolamide has a particular benefit to improve impaired sleep at high altitude (42). With ascent to altitude above 4000 m development of periodic breathing is nearly present in all people. Periodic breathing refers to an oscillating pattern in which increased respiration driven by hypoxia is followed by periods of apnea due to the development of hyperventilation-induced hypocapnia. This pattern leads to sleep fragmentation with frequent arousals, decreased total sleep time, and a feeling of not being refreshed in the morning. Acetazolamide markedly reduces periodic breathing at altitude and is associated with a diminution of apnea-induced falls in arterial oxygen saturation and improvement in subjective sleep quality. The beneficial effect of the drug has been attributed to inhibitory effects on peripheral chemoreceptors such that overshoots in the ventilatory response to hypoxia and hypercapnia are minimized.

Acetazolamide is well tolerated and is often taken by climbers for the entirety of their ascent. Side effects include increased urination and mild paresthesia of fingers and toes. Dexamethasone administered at a dose of 4 mg every 8 to 12 hours is also effective in preventing AMS although the mode of action is not known (43,44). Some individuals describe a euphoric effect and a greater sense of feeling refreshed. Dexamethasone should not be used for more than

one or two days for this purpose given the potential of the drug to cause glucose intolerance or acute psychosis.

Once AMS develops conservative management can be employed to include rest and avoidance of further ascent until symptoms resolve. Headache can be treated with acetaminophen or a nonsteroidal anti-inflammatory drug. Acetazolamide and dexamethasone have been shown effective in reducing the symptoms of AMS (45,46). In patients who fail to respond to more conservative therapy or those with any sign of cerebral or pulmonary edema should be given supplementary oxygen and descend immediately.

High Altitude Pulmonary Edema

High altitude pulmonary edema (HAPE) is a non-cardiogenic form of pulmonary edema that is potentially fatal. As with AMS, the risk for developing this complication is related to the rate of ascent and the absolute altitude obtained. With a gradual rate of ascent to 4500 m less than 1% of people develop HAPE while the incidence increases to 6% with rapid ascent (1,33). At an altitude of 5500 m the incidence rates vary between 2 and 15%. Cold temperature, a recent upper respiratory tract infection, and increased exertion all increase the risk for development of this disorder.

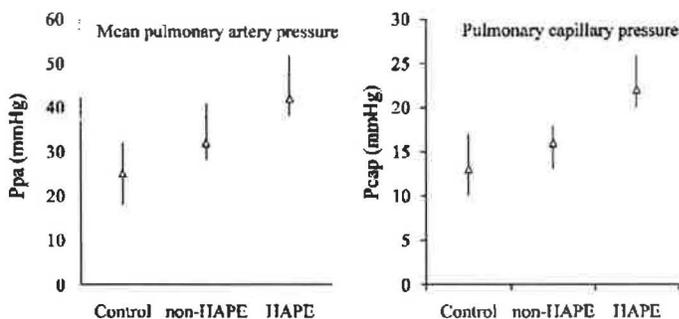
The initial manifestations of HAPE are decreased performance, dyspnea out of proportion to the level of exertion, and insidious development of a dry cough that eventually becomes productive of frothy often rusty sputum. Symptoms of AMS are often present but HAPE can develop explosively in the absence of other complaints. Physical findings include fever, tachycardia, tachypnea, and rales on auscultation. Chest radiography typically shows a normal sized cardiac silhouette and patchy diffuse infiltrates in both lung fields. Signs and symptoms of HAPE typically begin within the first 48 hours of arrival to a new altitude and only rarely develop after 4 days in the absence of further ascent. HAPE accounts for most deaths at high altitude, in part, because early signs can be mistaken for the expected shortness of breath at high altitude and the chronic cough often present due to the irritative effect of dry air.

People with a prior history of HAPE at a given altitude are at markedly increased risk for redevelopment of the disorder upon re-exposure to a similar altitude suggesting an underlying susceptibility.

While there is a considerable degree of overlap, an exaggerated vasoconstrictor response of the pulmonary vasculature to hypoxia exists in those prone to HAPE. Susceptible individuals demonstrate an unusually large increase in pulmonary artery pressures soon after arrival to altitude and prior to the onset of HAPE. In patients with HAPE, cardiac catheterization studies prior to treatment or descent have shown mean pulmonary artery pressures ranging from 60-80 mmHg with some as high as 117 mmHg.

HAPE is Associated with ↑ Pulmonary Artery and Capillary Pressure

16 HAPE prone compared to 14 controls after rapid ascent to 4559 m



Pulmonary transcappillary escape not significantly different (radiolabeled transferrin)

Circulation 103:2078-2083, 2001

Pulmonary artery wedge pressures are typically normal or only slightly increased and right ventricular filling pressures are normal. HAPE prone subjects at sea level exposed to brief periods of hypoxia or during exercise with normoxia exhibit a greater increase in pulmonary artery pressure as compared to normals suggesting a constitutively generalized hyperreactivity of the pulmonary circulation (50,51).

HAPE prone subjects have also been described to have a low hypoxic ventilatory response (52,53). A blunted response will cause alveolar P_{O_2} to be lower for any given altitude providing a further stimulus for hypoxia-induced pulmonary vasoconstriction. Lung volumes have also been reported to be reduced by 10-15% in HAPE-susceptible individuals. Assuming a proportional reduction in vascularity, less capacity for vascular recruitment in response to hypoxia can further contribute to higher pulmonary pressures (54).

While the degree of hypoxia-induced pulmonary vasoconstriction is profound studies show it is not uniform but rather patchy in its distribution. This heterogeneity in vasoconstriction predisposes to overperfusion and excessive rises in pressure in those regions of the lung that are less vasoconstricted. With use of magnetic resonance imaging techniques, HAPE prone subjects exhibit a greater degree of pulmonary blood flow heterogeneity in response to normobaric hypoxia as compared to HAPE-resistant individuals consistent with uneven hypoxic vasoconstriction (55,56). A similar inequitable distribution of blood flow occurs in pigs subjected to hypoxia as measured by the distribution of fluorescent microspheres (57). Diversion of flow from areas with strong hypoxic pulmonary vasoconstriction to areas with a weaker response may contribute to pressure increases sufficient to cause capillary leak and account for the patchy nature of infiltrates observed in radiographic images of the lung.

Excessive rises in intracapillary hydraulic pressure in relatively vasodilated areas is thought to be the primary mechanism behind the development of alveolar fluid accumulation. Samples taken during bronchoalveolar lavage show the fluid is protein rich and contains red blood cells. The threshold systolic pulmonary artery pressure for the appearance of albumin and red blood cells is 35 and 60 mmHg respectively (56). There are few inflammatory cells or markers suggesting the process is a high permeability form of edema. Inflammatory changes are only a late finding and thought to be a nonspecific response to the extravasation of fluid and cells into the alveolar space as opposed to playing a primary role in the pathogenesis of the disorder.

Histologic studies of lung tissue in rabbits and rats subjected to high capillary transmural pressures show disruption of the capillary endothelium and alveolar epithelium (59-61). These histologic changes rapidly reverse upon lowering of capillary pressure consistent with the rapid improvement in clinical status when HAPE-patients are moved to a lower altitude. Given this rapid response, alveolar fluid accumulation in early HAPE may simply be the result of pressure-mediated opening of pores or fenestrae or represent transcellular vesicular flux as opposed to damage to the capillary-alveolar barrier.

Strenuous exercise is a significant contributing factor for development of HAPE and may play a role in the development of the disorder at low or moderate altitudes. Even in otherwise healthy athletes with no history of HAPE, bronchoalveolar lavage fluid shows a significant increase in protein concentration and number of red blood cells following exercise at altitude (3810 m) as compared to samples taken at sea level (62). Significant increases in cardiac output can play a role in this effect by further increasing pressure in overperfused areas and possibly worsening the regional heterogeneity of blood flow. It is interesting to speculate that the fall in

cardiac output which normally occurs with acclimatization is an adaptive response to limit the increase in pulmonary capillary pressures.

Another factor present in those prone to HAPE is a diminished capacity to reabsorb alveolar fluid (63). Alveolar fluid reabsorption is normally driven by active transepithelial Na^+ transport across the alveolar cell. Na^+ moves across the apical membrane via an amiloride sensitive cation channel and then is extruded across the basolateral membrane by way of the $\text{Na}^+-\text{K}^+-\text{ATPase}$. The movement of Na^+ from lumen to interstitium generates an osmotic gradient which then favors the subsequent movement of water from the alveolar space into the interstitium and ultimately the capillary. Hypoxia exerts an inhibitory effect while β -adrenergic stimulation enhances this process. Due to the similarity of the Na^+ channel in the nasal epithelium to that in the alveolus, measurement of the nasal transepithelial potential difference has been used as an in vivo measure of transalveolar Na^+ transport.

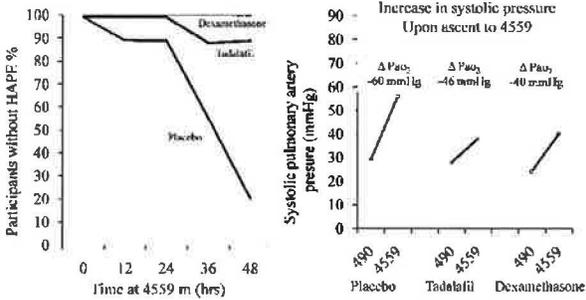
In a prospective double blind study, mountaineers with a history of HAPE were randomly assigned to prophylactic treatment with inhaled salmeterol or placebo in order to determine whether a β -adrenergic agonist would reduce the frequency of pulmonary edema in a susceptible population (64). Metered dose inhaled therapy was initiated on the day ascent to 4559 m was given every 12 hours throughout the study. Over the course of 2 days and nights at high altitude salmeterol significantly reduced the clinical and radiographic development of pulmonary edema as compared to placebo. The placebo treated subjects also had a greater degree of arterial hypoxemia and more marked symptoms of AMS.

Measurement of the nasal transepithelial potential difference was also measured and compared between the HAPE-prone subjects and normal controls at low altitude (64). In otherwise normal subjects this value is known to decline with gain in altitude consistent with an inhibitory effect of hypoxia. The HAPE prone subjects had significantly lower values when compared to the control group. A reduced baseline capacity to remove alveolar fluid combined with inhibitory effects of increasing hypoxia may importantly contribute to the fluid accumulation in HAPE prone subjects. Increasing alveolar Na^+ transport through β -receptor stimulation may be a novel pharmacologic approach to limit the degree of alveolar fluid accumulation.

The most effective means to reduce the risk of HAPE is a slow graded ascent and avoidance of strenuous exertion. Pharmacologic therapy may be considered in those with a prior history or repetitive episodes. These drugs act to attenuate the exaggerated hypoxic pulmonary vasoconstriction and lower pulmonary artery pressure. In a prospective randomized trial of mountaineers with prior HAPE, 20 mg of slow released nifedipine administered every 8 hours significantly reduced the risk of pulmonary edema as compared to placebo over the course of 3 days at 4559 m (65). This beneficial effect occurred in association with greater reductions in pulmonary artery systolic pressure as well as symptoms of AMS.

A number of observations suggest the exaggerated rise in pulmonary artery pressure with altitude in HAPE prone subjects is due to decreased bioavailability of nitric oxide (63,66,67). For example, in comparison to HAPE-resistant subjects, exhaled nitric oxide is decreased in HAPE prone subjects when measured at an altitude of 4559 m as well as during four days of hypoxic exposure at low altitude. In HAPE prone mountaineers studied at an altitude of 4559 m, inhalation of nitric oxide produced a decrease in mean systolic pulmonary artery pressure that was three times larger than the decrease in resistant subjects (66). Arterial oxygenation

Dexamethasone and Tadalafil ↓ Incidence of HAPE and ↓ Systolic PA Pressure



AMS significantly reduced with dexamethasone and not tadalafil vs placebo, all subjects with HAPE had AMS

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prophylactic therapy in reducing the risk of HAPE in subjects with a previous history of the disorder (68). This decrease in risk is accompanied by a reduction in pulmonary artery pressure similar in magnitude to that of tadalafil. Dexamethasone increases nitric oxide availability by increasing endothelial nitric oxide synthase expression. In addition, dexamethasone stimulates surfactant secretion which tends to reduce alveolar surface tension and microvascular transmural pressure. Furthermore, the drug increases alveolar fluid clearance mediated by upregulation of the alveolar apical membrane Na^+ channel and basolateral $Na^+-K^+-ATPase$.

Once HAPE develops the primary goal of therapy is to increase alveolar and arterial oxygenation. This is best accomplished by moving the patient to a lower altitude and administering supplemental oxygen. As a temporizing measure simulated descent can be accomplished with a portable hyperbaric chamber sometimes referred to as a Gamow bag. This bag is air-impermeable and completely encloses the patient. The bag is inflated with a foot pump to 2 psi (105 mmHg) above ambient pressure. At an altitude of 4250 m (14000 ft) this pressure will simulate an elevation in the bag of roughly 2100 m (7000 ft) and result in marked improvements in oxygen saturation.

After an episode of HAPE particular caution needs to be employed when returning to altitude. A slower rate of ascent and early recognition of the signs and symptoms of altitude illness should be emphasized. Prophylactic therapy with a slow release formulation of nifedipine will decrease this risk. A recent case report described a climber with HAPE who successfully summited Mt. Everest less than three weeks after clinical recovery using prophylactic therapy with sildenafil, salmetrol, and acetazolamide (69). Patients with recurrent episodes or those who develop HAPE at an altitude below 2500 m may have a baseline condition causing increased pulmonary artery pressure such as mitral valve stenosis, a pulmonary or intracardiac shunt, or unilateral absence of a pulmonary artery (70).

High Altitude Cerebral Edema

High altitude cerebral edema (HACE) is a potentially fatal neurologic disorder caused by hypoxia that typically occurs during rapid ascent to high altitude. In virtually all cases the disorder is preceded by AMS suggesting the conditions are two ends of a spectrum resulting from a similar pathophysiologic process. Patients with AMS can rapidly develop HACE when

improved following inhalation therapy in a subset of subjects who had radiographic evidence of pulmonary edema. HAPE prone subjects exhibit a blunted endothelium-dependent vasodilator response to acetylcholine under conditions of hypoxia in comparison to normal controls (67). Restoring nitric oxide bioavailability likely explains the efficacy of tadalafil administered at a dose of 10 mg twice daily in preventing HAPE and lowering systolic pulmonary artery pressure in susceptible individuals (68).

Dexamethasone administered at a dose of 8 mg twice daily is also effective as

arterial oxygenation deteriorates due to development of pulmonary edema. HACE rarely occurs below 4000 m and the prevalence at 4000-5000 m is estimated to be 0.5 to 1.5% (33).

HACE is a clinical diagnosis characterized by the onset of progressive truncal ataxia and increasing confusion. In some cases mood changes and hallucinations are noted. Seizures are uncommon. Physical findings include papilledema, retinal hemorrhage, and occasionally sixth cranial nerve palsy resulting from increased intracranial pressure. Over the course of one to two days and in the absence of treatment patients can develop coma and ultimately die as a result of brain herniation. Cognitive changes consistent with HACE are commonly present in climbers of Mt Everest who die on the mountain (71).

The precise mechanism by which edema develops in this disorder is not known with certainty. In a series of nine patients with HACE magnetic resonance imaging studies of the brain were obtained from 16 to 132 hours (mean 58 hours) after the clinical diagnosis (72). In seven subjects there was increased T2 signal intensity particularly in the corpus callosum and centrum semiovale. The absence of grey matter lesions lead the investigators to conclude a vasogenic mechanism was responsible for edema since the orderly structure of white matter makes it more prone to injury from vasogenic causes. By contrast cytotoxic edema affects both grey and white matter but especially the former.

Autopsy studies of individuals with HACE and MRI images in survivors of the disorder have also shown evidence of microhemorrhages (73). The imaging studies found the areas of hemorrhage were mostly in the corpus callosum. In some patients the lesions were still evident several months after the initial clinical presentation. These types of lesions in other settings have been indicative of obstruction to venous outflow suggesting a similar process may also be present in HACE patients. Hypoxia induced cerebral vasodilation along with impaired autoregulation could lead to overperfusion and increased hydrostatic pressure in cerebral microvascular beds resulting in capillary leakage and consequent edema. Increases in venous pressure would be expected to exacerbate this vasogenic mechanism of edema formation.

There may also be a cytotoxic component to edema formation in HACE (74). Diffusion weighted magnetic resonance imaging studies suggest swelling of astrocytes possibly mediated by oxygen radical-induced pump failure of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ formation.

As with the other forms of altitude illness the primary treatment of HACE is descent to a lower altitude as quickly as possible. Supplemental oxygen should be administered. Although not well studied, dexamethasone is routinely given in this setting starting with a loading dose of 8 mg (orally or intramuscularly) followed by 4 mg every 6 hours. Several hours in a portable hyperbaric chamber can be life saving while descent is being arranged.

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