Pulmonary Complications of High Altitude Exposure

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The first written report of mountain sickness originated in China sometime around 37 to 32 B.C. [1] during the reign of emperor Chung Ti of the Western Han Dynasty when a high official advised the emperor against sending an escort of about one hundred people to Ke-pin (what is today Afghanistan):

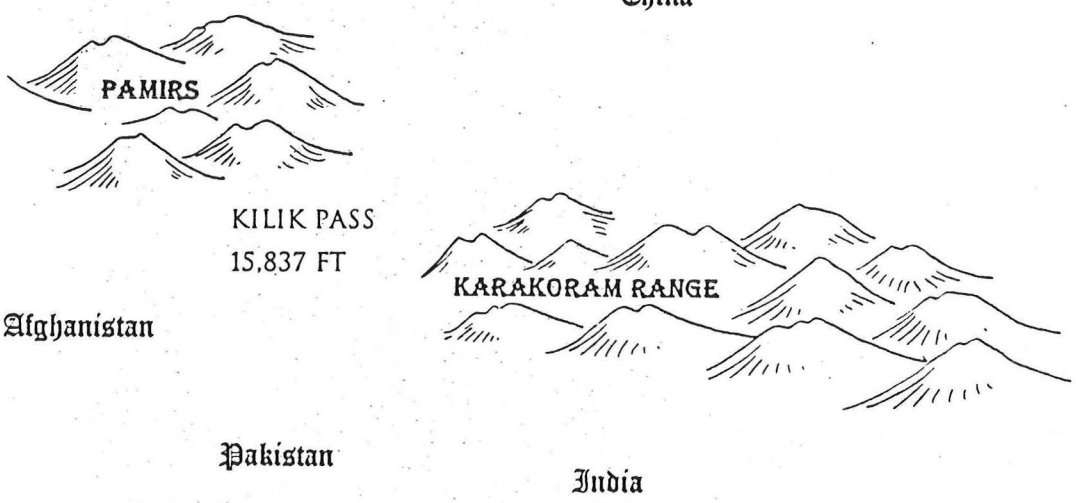
> "...Next, one comes to Big Headache and Little Headache Mountains, as well as Red Earth and Swelter Hills. They make a man so hot that his face turns pale, his head aches, and he begins to vomit. Even the donkeys and swine react this way."

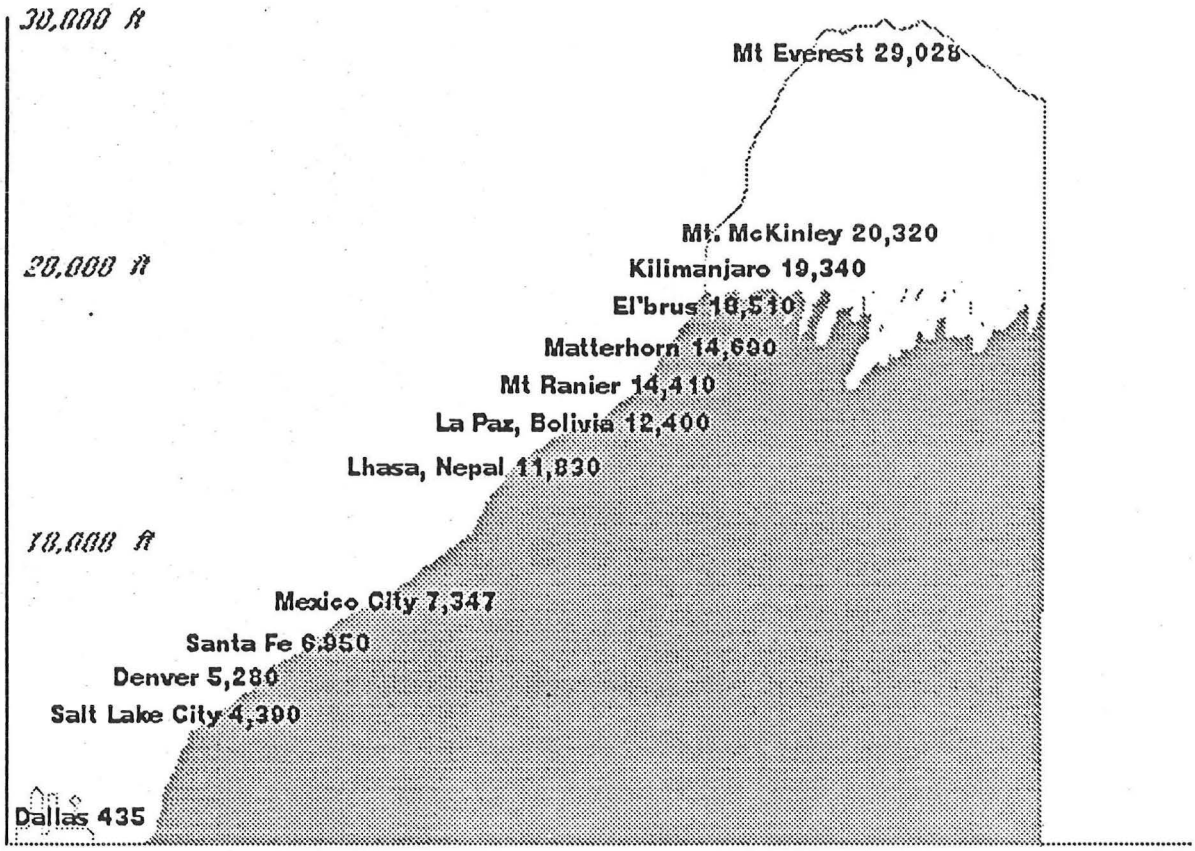
Historians believe that the route described in this text is the Kilik Pass in the western edge of the Himalayan Karakoram Range or in the Pamirs at an altitude of 4,827 m or 15,837 ft. At this level, the barometric pressure (P_B) would be approximately 430 Torr. The corresponding tracheal oxygen partial pressure saturated with water vapor would be about 80 Torr [2].

The next reported incidence of altitude sickness also occurred in this area at about 403 A.D. by a Chinese monk traveling in Kashmir and Afghanistan. He noted that his companion foamed at the mouth and died as they were ascending a mountain pass [1]. Surprisingly few written reports of this illness are found subsequently until 1590 A.D when the clinical syndrome was described in the South American Andean Mountains [3]. In the 19th century Paul Bert showed that the symptoms of acute mountain sickness were primarily the consequence of the low partial pressure of oxygen rather than the low atmospheric pressure *per se* [4]. Relative ignorance of high altitude physiology persisted well into the 20th Century. In 1925 J. Barcroft wrote that

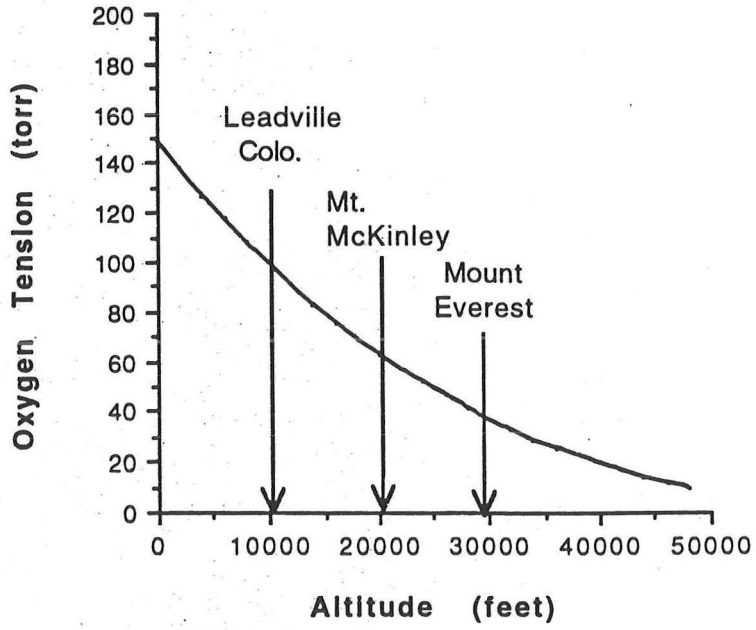
> " the acclimatized man.....does not exist. All dwellers at high altitudes are persons of impaired physical and mental powers." [5]

World War II marked the beginning of the revolution in our understanding of physiological effects of high altitude; attempts to study and improve the performance of fighter pilots and soldiers conducting mountain warfare led directly to the founding of modern respiratory physiology.





Inspired Oxygen Tensions at High Altitudes



Physical Effects of High Altitude		Consequence for the Lung
Low partial pressure of oxygen	→	Hypoxemia
Low air density	→	Low air flow resistance
Low air temperature and humidity	→	Airway cooling and drying

Exposure to hypoxia affects all steps of the oxygen transport chain; these steps are listed below:

Steps in the oxygen transport chain

Ventilation

Alveolar-capillary Gas Exchange

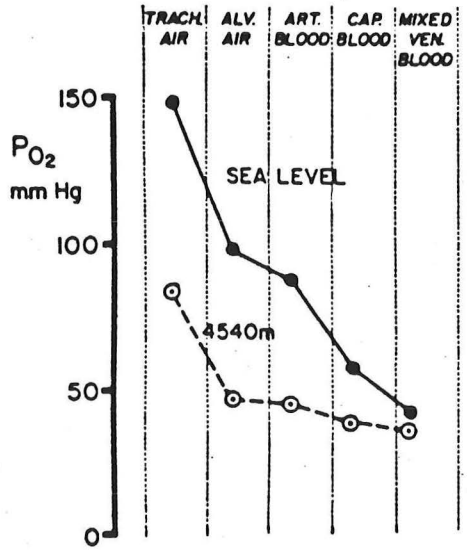
Cardiac output

Oxygen carrying capacity

Peripheral Tissue Diffusion

Mitochondrial volume and enzyme content

Oxygen cascade from inspired air to tissue at sea level and altitude



At sea level, PO_2 drops by more than 100 torr from inspired air to mixed venous blood. In an acclimatized person at high altitude, this drop is attenuated so that the mixed venous

PO_2 is is only slightly lower than at sea level. This attenuation of the drop in PO_2 along the oxygen cascade reflects physiological adjustments in each step of the oxygen transport chain. Figure from Weil [6].

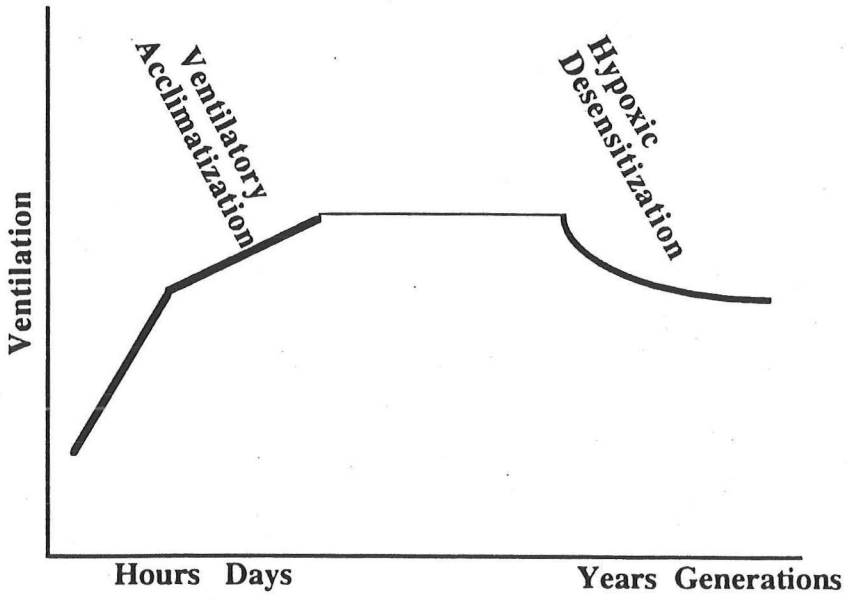
Physiological Effects of High Altitude on the Pulmonary System

1. Ventilatory Control: Hyperventilation
   Periodic Breathing
2. Impaired Gas Exchange
3. Pulmonary Arterial Hypertension
4. Lung Growth and Development

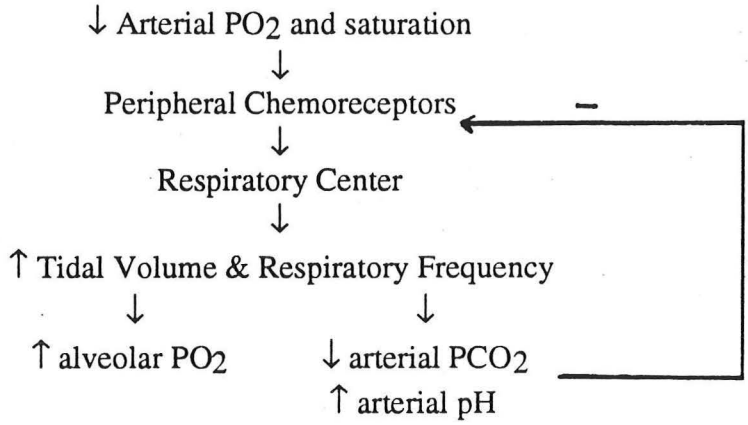
Time Course of Ventilatory Changes

Acute exposure:	minutes to hours
Short-term adaptation:	days to weeks
Chronic adaptation:	months to years
High altitude natives:	generations

Time Course of Ventilatory Adjustment to Altitude [6]



Acute Ventilatory Response to High Altitude Exposure

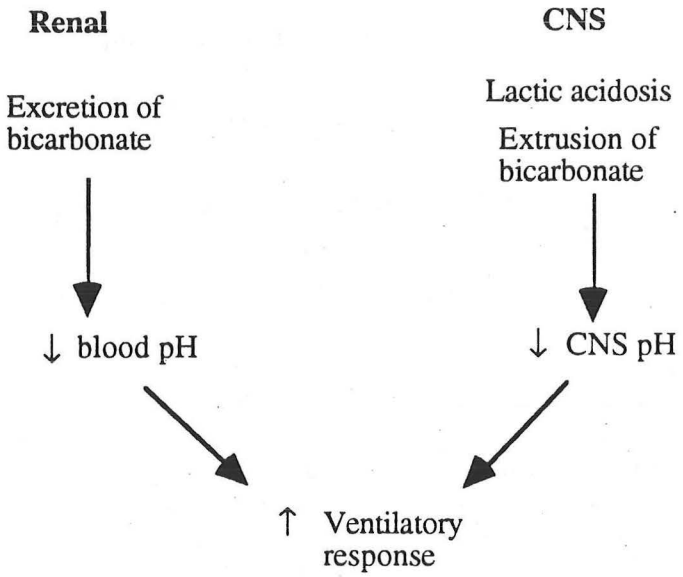


In normal individuals at sea level, ventilation is mainly regulated by the arterial partial pressure of carbon dioxide ($PaCO_2$) with hypoxia being a secondary regulatory stimulus. In conditions where oxygenation is impaired, the hypoxic ventilatory response becomes increasingly more important as a survival mechanism. Acute ascent to altitude produces an immediate **increase in ventilation**. The stimulus is a fall in inspired partial pressure of O_2 leading to a reduced arterial O_2 tension (PaO_2) and a reduced arterial O_2 saturation (SaO_2). The hypoxic stimulus acts mainly on the peripheral chemoreceptors, ie. the carotid and aortic bodies, and result in augmentation of tidal volume and to a less extent an increase in respiratory frequency. A decrease in arterial O_2 content with a normal PaO_2 (as in anemia or carbon monoxide poisoning) will not produce ventilatory stimulation [7, 8].

This hypoxic ventilatory response is an inborn characteristic that varies among individuals and is under strong genetic control [9, 10]; it is positively correlated with the degree of exercise hyperventilation and can be augmented by exogenous progesterone [11, 12] and abolished by resection of the carotid body [13, 14]. At high altitude the hypoxic ventilatory response will attenuate the drop in alveolar PO_2 (PAO_2) [15]. However, the advantageous effect on oxygenation is offset by the adverse effects on acid-base homeostasis due to the rapid development of **hypocapnia** and **respiratory alkalosis**, which in turn inhibit the ventilatory response to hypoxia though its actions on both the carotid body and central chemoreceptors, and may contribute to altered CNS function.

The acute biologic dilemma is how to balance tissue oxygenation against CO_2 and H^+ homeostasis since renal compensation requires days to achieve. Physiologically a compromise is reached, ie. alveolar PO_2 is only partially returned to normal and the acid-base disturbance less severe than might occur if a full ventilatory response to hypoxia is allowed.

Subacute Ventilatory Response to High Altitude Exposure



Over several days at a given altitude, there is a further slower but progressive rise in ventilation associated with a further decrease in $PaCO_2$ in a process termed "**ventilatory acclimatization**". An altitude that evokes little acute increase in ventilation may evoke a marked response several days later. Also the increase in ventilation cannot be rapidly reversed by acute administration of oxygen. The underlying mechanism remains poorly understood despite a staggering amount of investigation.

The major factor responsible for ventilatory acclimatization is a gradual normalization in arterial pH by renal excretion of HCO_3^-, thus removing the inhibitory effect of alkalosis on the respiratory center. However, arterial pH normalization is not always correlated with the increase in ventilation at altitude [16]. It is also possible that an active transport mechanism via carbonic anhydrase can excrete HCO_3^- out of the CNS so that pH of the CNS interstitial fluid may be normalized even when arterial blood pH remains alkalotic; this might explain the increased ventilation during acclimatization [17]. In animal studies high altitude exposure is associated with a reduced cerebral blood flow resulting in increased CNS lactate production and a low pH in the cerebral interstitial fluid which is not reflected in the pH of the CSF or blood [18, 19]. This relative CNS interstitial acidosis may stimulate the respiratory center and account for the sustained hyperventilation at altitude. The relative importance of regional CNS acid-base regulation in acclimatization is uncertain and is an area of current controversy [20-23].

Chronic Ventilatory Response to High Altitude Exposure

(Years to Generations)

↓ Ventilatory drive to hypoxia and hypercapnia

↓ Ventilation

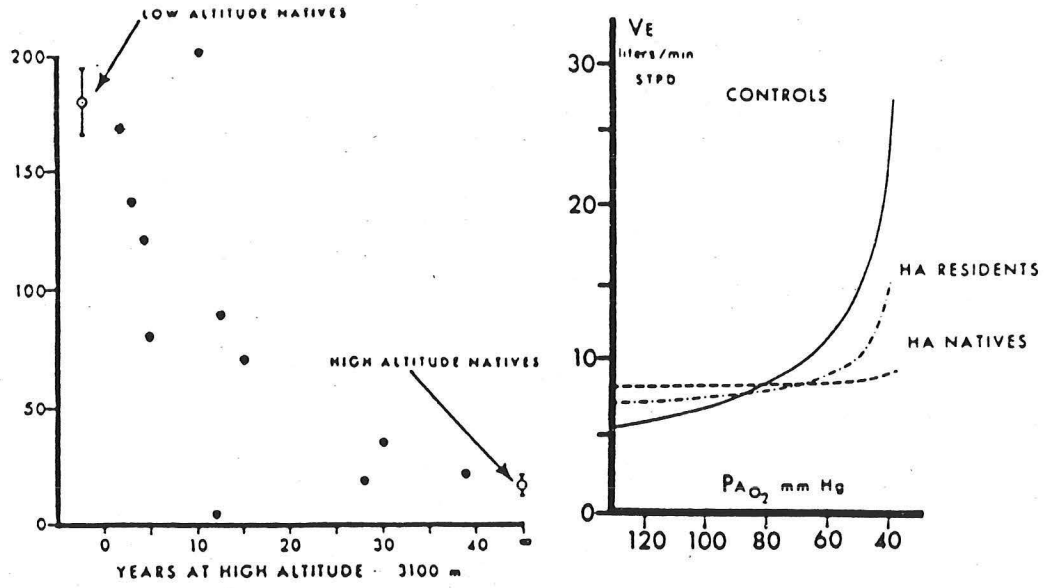
↑ Arterial PCO_2

Rapid shallow breathing pattern

Paradoxical hyperventilation at low altitude

After acclimatization, ventilation remains stable at an elevated level for many years. However, it is then followed by a phase of relative hypoventilation and loss of the normal ventilatory drive to hypoxia; this change is termed "**hypoxic desensitization**" and is associated with a lower ventilation and rising arterial PCO_2.

HYPOXIC VENTILATORY RESPONSE



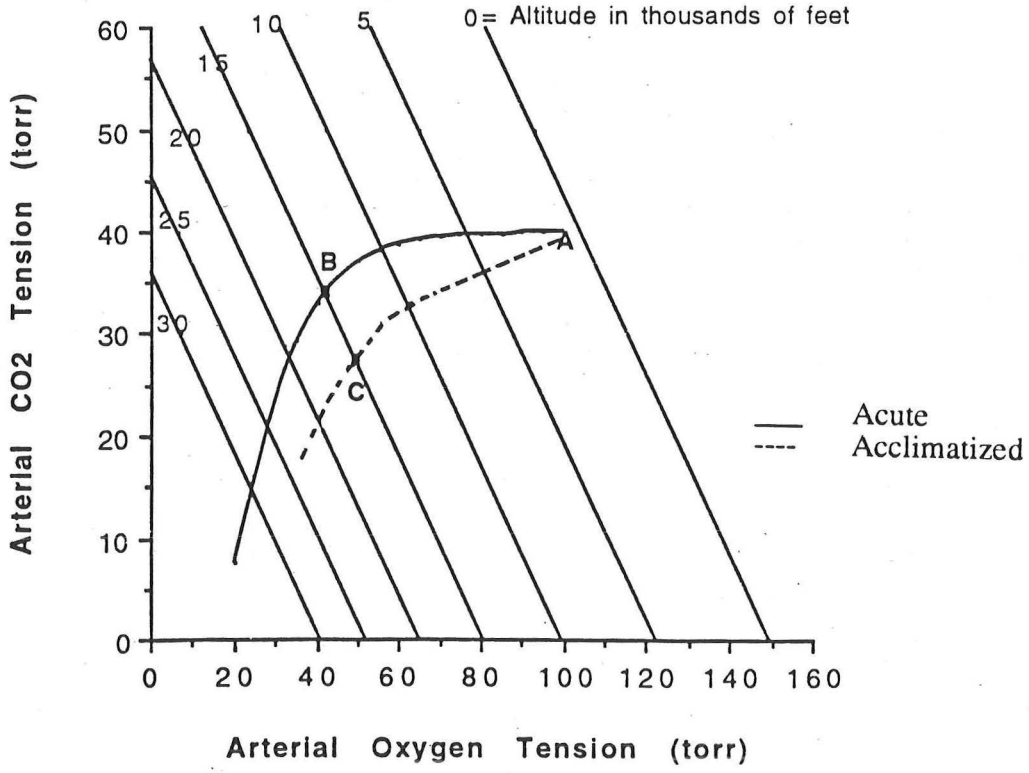
From Weil, et al [24, 25]

Hypoxic desensitization is not unique to altitude exposure; it can be seen in patients with cyanotic congenital heart defects. It is acquired after many years of hypoxic exposure. Studies in the Peruvian Andes and the rocky Mountains show that hypoxic responses are normal in young children native to high altitude and only begin to be depressed during late childhood or early adulthood [26-28]. The rapidity of onset of hypoxic desensitization is probably related to the degree of ambient hypoxia. Once established, hypoxic desensitization appears to be irreversible; high altitude natives after months to

years of living at low altitude still had attenuated hypoxic responses similar to those observed at high altitude [29, 30]. In contrast, in patients with congenital heart defects, hypoxic desensitization is sometimes reversible after surgical correction [31]. This different response may reflect the longer duration of hypoxic exposure in native highlanders. Hypoxic desensitization is most likely mediated through CNS respiratory center and not peripheral chemoreceptors [32, 33], although the precise mechanism is still unclear.

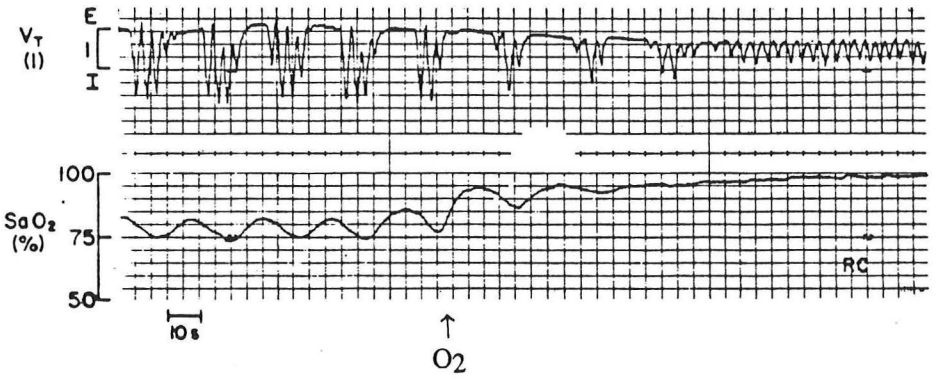
In otherwise normal long term high altitude residents, a reduced hypoxic ventilatory response does little harm and may signal the development of other adaptations that maintain oxygen delivery without the need for greater ventilation (eg. increased densities of capillaries, mitochondria and capacity for oxygen extraction by peripheral tissues). However, in a small percentage of altitude residents, the loss of hypoxic ventilatory drive may signify the development of chronic mountain sickness (discussed later); and in patients with lung disease it may lead to progressive respiratory failure.

Normal Arterial PO_2 and PCO_2 at High Altitude



With acute exposure to high altitude, eg. 15,000 ft., the normal relationship between arterial PCO_2 and PO_2 follows the upper curve from point **A** to **B**, ie. both PO_2 and PCO_2 decline. With acclimatization at the same altitude, the relationship shifts to the lower curve, from point **B** to **C**, ie. arterial PCO_2 declines further and arterial PO_2 is higher. After many years at high altitude, the relationship drifts somewhere in between these 2 curves.

Periodic Breathing at High Altitude



Tracings of periodic breathing from [34]

Periodic breathing is a repetitive cyclic pattern of breathing with or without periods of apnea; one form of it is commonly known as the Cheyne-Stokes respiration associated with congestive heart failure and CNS disease.

Periodic breathing is a common finding in normal subjects sleeping at high altitude and can also be demonstrated in the awake state; it is typically worse on the first two nights and usually much improved by the fourth or fifth night. Complaints include poor sleep quality, vivid dreams, frequent arousal and feeling of suffocation. Subjective complaints are consistently out of proportion to the objective findings. Sleep studies typically show an increase in light stages of sleep (stages 1 and 2), a decrease in deeper stages (3 and 4) and frequent arousal compared with sleep at sea level. There is usually no change in the amount of rapid eye movement (REM) sleep [35]. Cycling of heart rate with periodic breathing is common, ie. tachycardia during hyperpnea and bradycardia during apnea [36].

Etiology of Periodic Breathing

Periodic breathing is an exaggeration of the normal cyclic variation in ventilatory drive. It is analogous to the thermostat of an air conditioner. Even though the room temperature is set at a given level, there will always be a cycling of temperatures around the set point depending on the time it takes for the thermostat to sense a given termperature change.

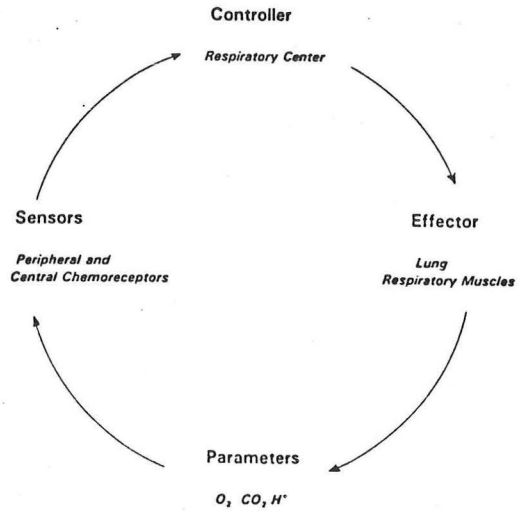
Normal breath to breath changes in PCO_2 and pH are sensed by the central chemoreceptors after a circulatory time delay of 8 to 10 seconds. This delay results in a phase difference between a given stimulus and the feedback response; the phase difference is exaggerated if the time delay is increased for any reason, eg. reduced cardiac output or cerebral blood flow. This delay would cause a periodic pattern breathing with a cycle equal to twice the time delay between the lung and the respiratory center. Normally the body provides a number of counter-balancing mechanisms that tend to minimize such fluctuations in chemoreceptor drive.

Mechanisms that Normally Minimize Ventilatory Fluctuations

1. There are large gas stores of O_2 and CO_2 in the lung; these stores would dampen out the breath to breath changes in arterial blood gases.

2. There is a short-term potention of after-discharges in neural synapses of the respiratory center; this potentiation also tends to prevent rapid fluctuations in chemorecptor drive.

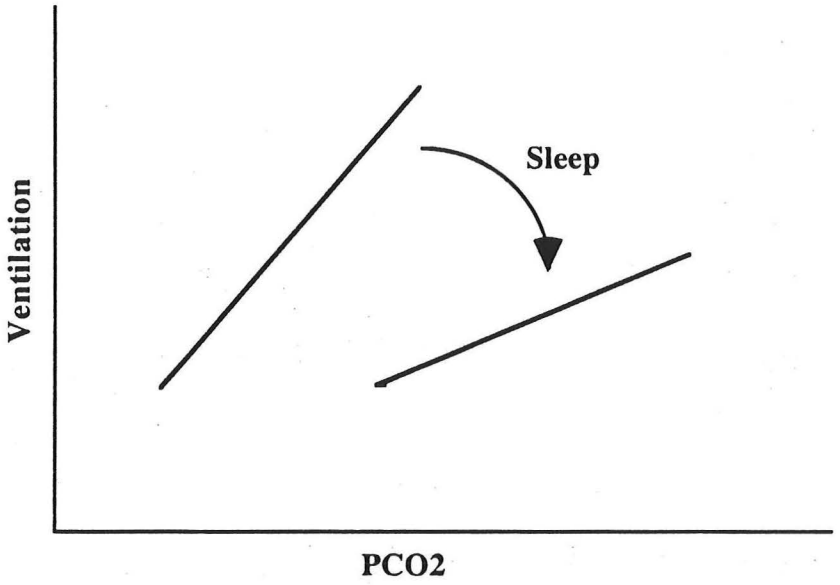
3. In the awake person there is cortical override that tends to maintain a constant level of ventilatory drive to CO_2 to counter-balance fluctuations in peripheral chemoreceptor discharge.



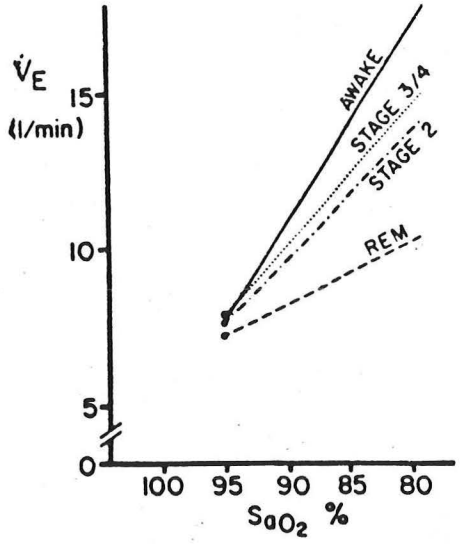
Factors Contributing to Periodic Breathing at High Altitude

Hyperventilation	↓ Gas stores in the lung
Hypoxemia	↓ CNS short term potentiation
Cerebral edema	↑ Time delay
Sleep	↓ Cortical override

At high altitude, the low barometric pressure and hyperventilation with a larger tidal volume tend to decrease gas stores in the lung. Hypoxemia stimulates carotidy body discharge and inhibits central short term potentiation of after-discharges. These changes remove the normal protective mechanisms that maintain a near constant level of ventilatory drive and lead to large fluctuations in chemoreceptor response. Cerebral edema often develops at high altitude and may compromise blood flow to the respiratory center and increase the time delay for sensing a given change in circulatory signals. Further, during sleep, cortical override is lost. All these factors contribute to the development of what amounts to an an overshoot of the normal ventilatory response to hypoxia (hyperpnea) and hypocapnia (hypopnea or apnea) leading to the cyclic breathing pattern.



Sleep suppresses the ventilatory response to CO_2. The threshold of ventilatory response to CO_2 is increased and the slope of the response is reduced.



Sleep, especially in the REM stage, also suppresses the ventilatory response to hypoxia. From Lahiri et al. [34].

Gas Exchange at High Altitude

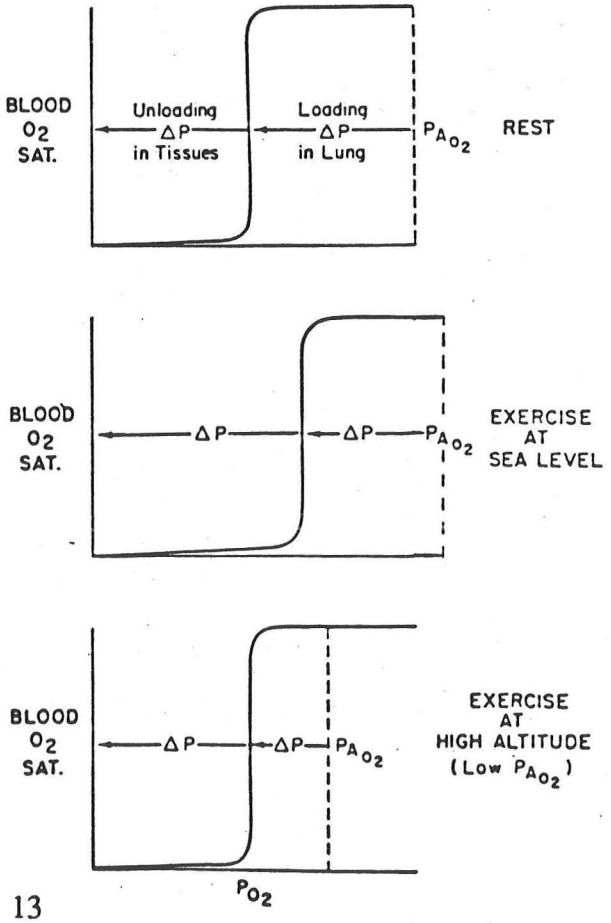
Impairment	Acute Compensation	Chronic Compensation
Low rate of O_2 diffusion + Ventilation-perfusion inhomogeneity ↓ ↓ arterial O_2 saturation	↑ ventilation ↑ cardiac output ↑ tissue O_2 extraction	Polycythemia ↓ O_2 affinity of hemoglobin ↑ tissue O_2 extraction lung tissue growth?

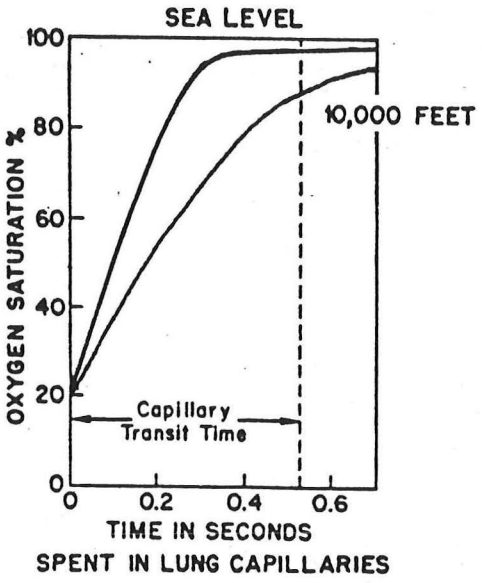
At sea level, the normal maximal rate of oxygen transport during exercise is primarily limited by the capacity of the cardiovascular system for oxygen delivery. At altitude, because of the low rates of oxygen transfer from alveolar gas to the blood, gas exchange in the lungs becomes increasingly important and is the rate-limiting step in O_2 transport at altitudes above 10,000 ft. At low alveolar oxygen tensions the rates at which oxygen can be driven across the alveolar capillary membrane and into red cells by diffusion and the rates of binding to hemoglobin are also reduced. As cardiac output and pulmonary blood flow increase during exercise, red cells may not remain in lung capillaries long enough for the oxyhemoglobin saturation to equilibrate with alveolar oxygen tension. Hence as exercise work load increases, oxygen saturation of blood leaving the lung will progressively decline.

Top: An exaggerated oxyhemoglobin dissociation curve is shown. At a given alveolar PO_2 (PAO_2), the pressure gradient (ΔP) from alveoli to blood drives diffusion into the lung and the gradient from blood to mitochondria (PO_2 close to zero) drives diffusion into the tissues.

Middle: At heavy exercise at sea level, acidosis and an increased body temperature shift the curve to the right, resulting in an accentuated gradient driving diffusion into tissues. Hyperventilation increases PAO_2, so the net gradient for O_2 loading in the lung is unchanged or only slightly reduced.

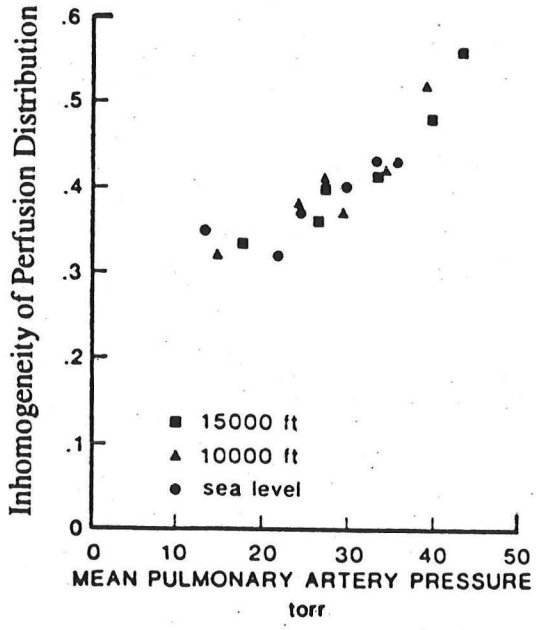
Bottom: During exercise at high altitude, hypoxia significantly reduces the pressure gradient for diffusion from alveolar air into lungs. Figures are from Johnson [37].

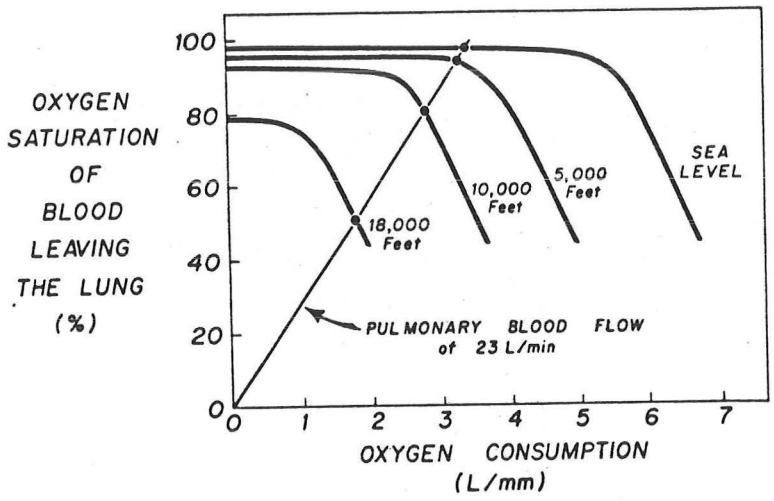




At sea level, red cells have plenty of time to fully oxygenate as they travel through the pulmonary capillary bed, even at peak exercise equivalent to a transit time of about 0.5 seconds. At 10,000 ft., the rate of oxygenation is reduced so full saturation cannot be achieved during the same transit time.

The matching of ventilation to perfusion in the lung is also impaired at high altitude; areas of abnormally low ventilation-to-perfusion ratio ($\dot{V}_A/\dot{Q}$) and shunt are frequently present and the degree of non-uniform matching of ventilation to perfusion is correlated with a rising pulmonary arterial pressure [39]. It is thought that this non-uniformity results from uneven regional hypoxic pulmonary vasoconstriction and perhaps the development of scattered patches of subclinical interstitial or alveolar pulmonary edema [39-41].

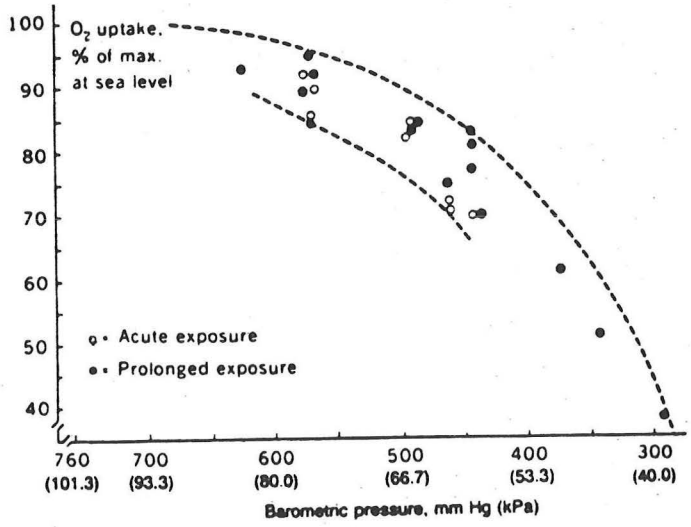




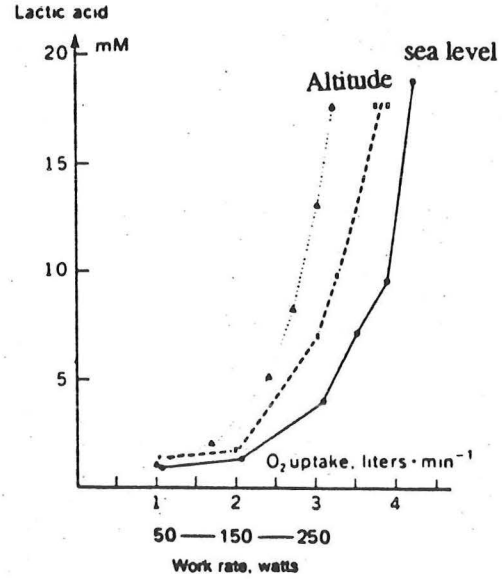
From Johnson [42]

Arterial O_2 saturation declines at progressively lower level of oxygen consumption with increasing altitude (above figure). This results in a progressively lower maximal oxygen uptake and relatively early onset of lactic acidosis during physical exertion at high altitude (below). Over a few days, erythropoiesis is stimulated, the affinity of hemoglobin for O_2 is reduced and tissue O_2 extraction is increased. It is still controversial as to whether cellular lung growth is stimulated by chronic hypoxia. These compensatory changes will be discussed later.

Maximal Oxygen Uptake



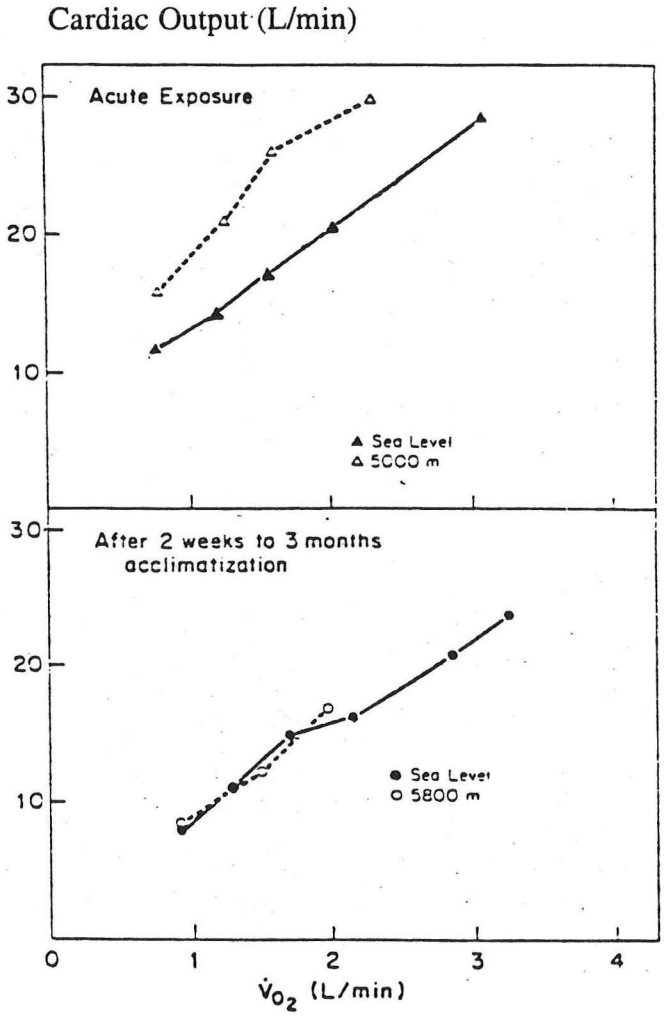
Lactic Acidosis

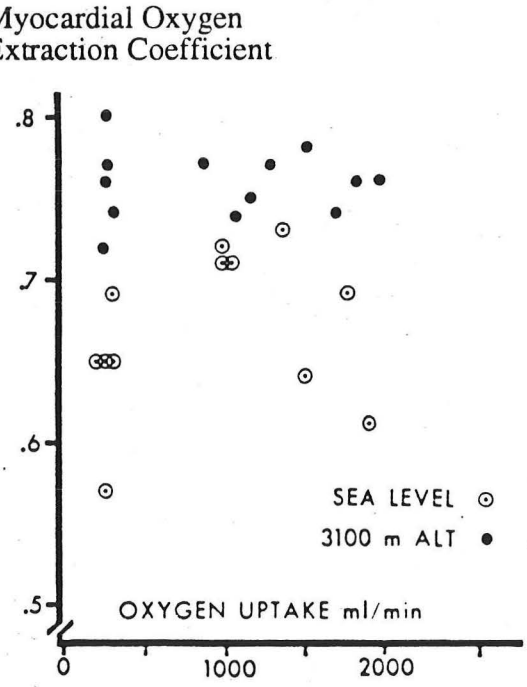


From Astrand and Rodahl [43]

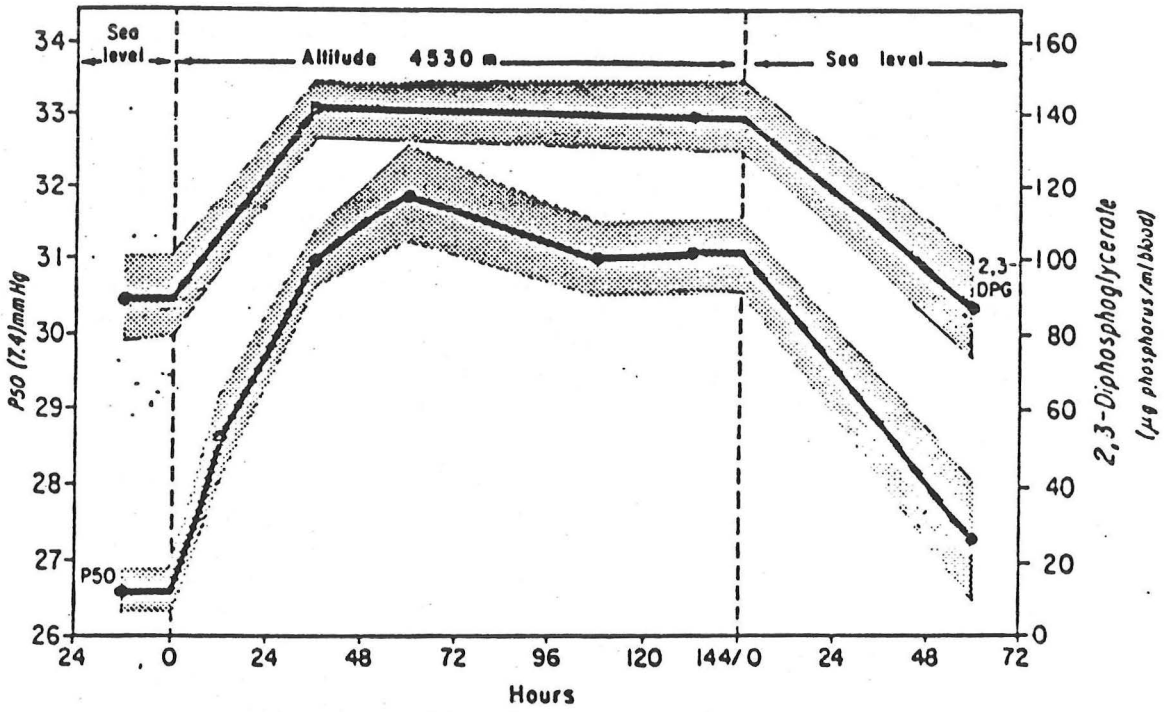
Cardiac Output and Peripheral Oxygen Extraction

Upon acute exposure to hypoxia, heart rate and cardiac output increase; peripheral vascular resistance decreases and systemic arterial pressure is unchanged. After several days at altitude, maximal stroke volume, cardiac output and skeletal muscle blood flow all decrease significantly to below sea level values; at the same time peripheral vascular resistance and systemic arterial pressure rise. In Operation Everest II, where exercise test were performed in normal subjects subjected to 40 days of simulated altitudes >8,000 m (P_B 240 torr), cardiac output at a given level of oxygen uptake was found to be relatively maintained; a reduction in stroke volume was balanced by a higher heart rate [44]. The drop in cardiac output is not due to a low myocardial contractility [45, 44] but is associated with a decreased ventricular filling (ie. decreased right atrial and wedge pressures), probably secondary to fluid shift out of the intravascular space leading to a reduced plasma volume. Breathing oxygen did not increase either stroke volume or heart rate for a given filling pressure. In another study, after 10 days at 3,100 m, coronary blood flow decreases by 32% but this effect is offset by a 28% increase in coronary arterial O_2 extraction, so myocardial O_2 delivery is maintained and myocardial hypoxia does not develop in the normal individual [46]. An intrinsic change in peripheral vascular tone has been postulated to explain the lower cardiac output but is unproven. Oxygen extraction by peripheral tissue is enhanced at high altitude [47].





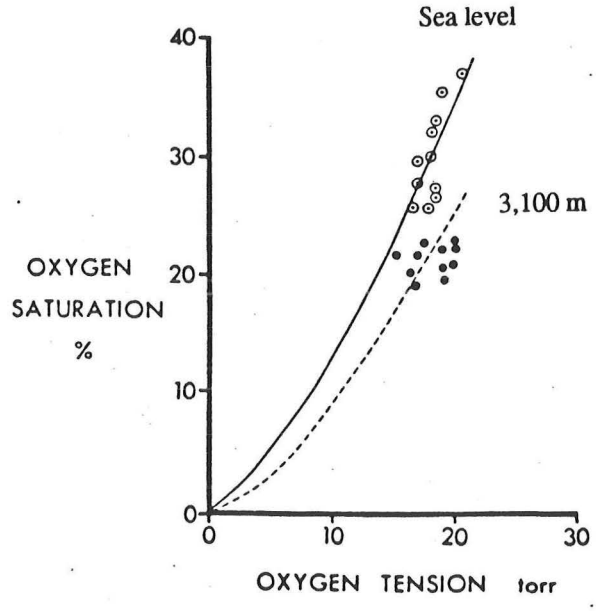
Affinity of Hemoglobin for Oxygen



P50 and 2,3-DPG from Lenfant et al [48].

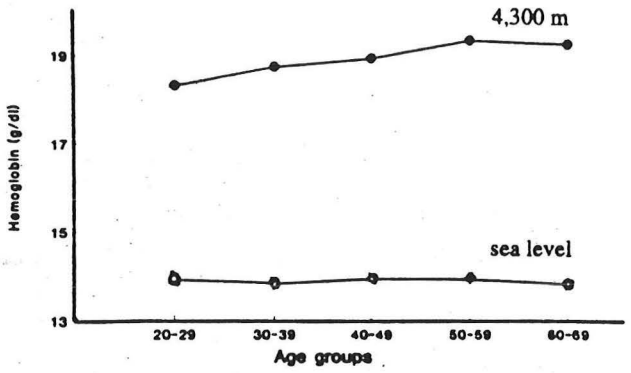
The red cell 2,3-diphosphoglycerate (2,3-DPG) concentration rises within the first 48 hours at altitude [48]. This increase helps to stabilize the hemoglobin molecule in the desaturated configuration, leading to a shift of the oxyhemoglobin curve to the right, ie. a higher PO_2 at which 50% of the hemoglobin is saturated with O_2 (P_{50}) measured at standard pH and PCO_2 or a reduced affinity for oxygen. This rightward shift is in part counteracted by the respiratory alkalosis which tends to shift the curve to the left. However, the *in vivo* position of the curve at rest is still right-shifted after 10 days at 3,100 m [46].

A net right shift of the oxyhemoglobin dissociation curve results in a lower O_2 saturation for a given O_2 tension at 3,100 m (closed circles) than at sea level (open circles).



Polycythemia at Altitude

During the first 7-10 days at high altitude, red cell volume increases and plasma volume decreases due to fluid shifts and perhaps release of marginated red cells from the spleen; this is reflected in an acute increase in hematocrit and hemoglobin concentration. True stimulation of erythropoiesis via hypoxic stimulation of erythropoietin production by the kidney occurs over the next 2 weeks or so and is sustained chronically. The increased red cell mass and volume help return oxygen delivery toward normal. Plasma viscosity and erythrocyte deformability are largely unaffected by altitude exposure [49]. Whole blood viscosity changes with hematocrit. Erythrocyte aggregation almost doubles within one day of arrival to 4,559 m and reflects an acute phase reaction [49].

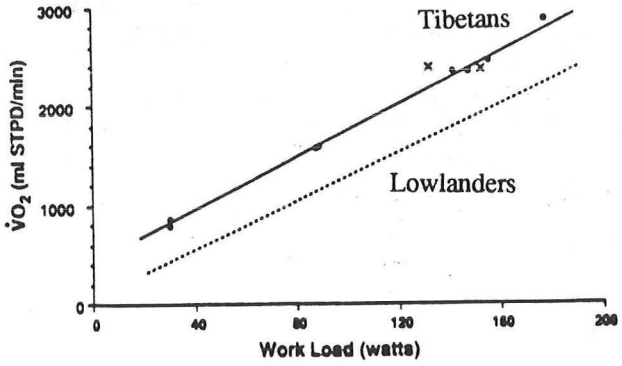


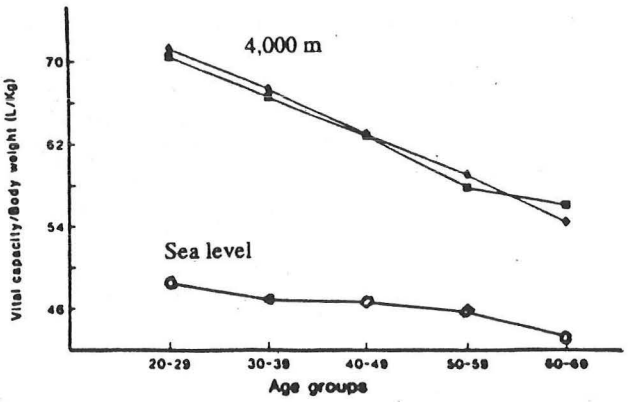
Mean hemoglobin concentrations in different age groups of miners who are long term residents either at sea level (open circles) or high altitude, 4,300 m (closed circles). From [50].

Growth and Development of the Lung at Altitude

Native populations at high altitude appear to adapt well to the hypoxic environment and can achieve higher rates of maximal oxygen uptake than native lowlanders acclimatized to a similar altitude, implying an increased capacity for oxygen transport and/or utilization by working muscle. One potential way of compensating for the slow rates of oxygen transfer across the alveolar capillary membrane at high altitude is to increase the size and surface area of the lungs for gas exchange. This possibility has been examined in both human and animal. It is well known that high altitude natives possess smaller stature with rounded and relatively large chests. Immature dogs raised to maturity at high altitude show higher diffusing capacities (DL_{CO}) and lung tissue volume than matched controls simultaneously raised at low altitude [51]. Infants born at high altitude have larger lung volumes and higher lung compliance than their sea level counterparts [52]. Adult native residents of high altitude also have larger lung volumes, diffusing capacities and lung compliance than lowlanders of the same age and race [53, 54, 50].

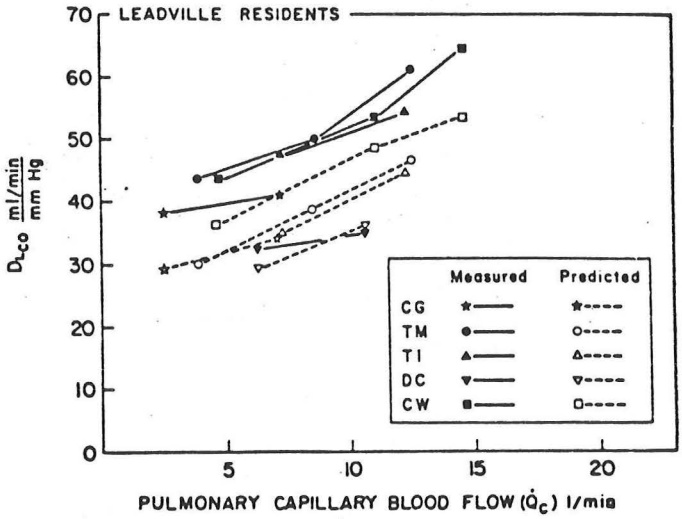
Moore and Sun [55] compared matched samples of young Tibetan men who are lifelong high altitude residents of Lhasa (>3,658 m, P_B 490 Torr) and who descended from a long-resident high altitude population with a non-native high altitude population consisting of Chinese Hans who had migrated as adults from lowland China to Lhasa on average 8 years previously. The two groups were matched for body size, health status, extent of exercise training and smoking history. The native Tibetans demonstrate higher exercise ventilation, vital capacity and maximal oxygen uptake. Both groups had higher maximal oxygen uptake for a given work load than sea level residents of the United States.



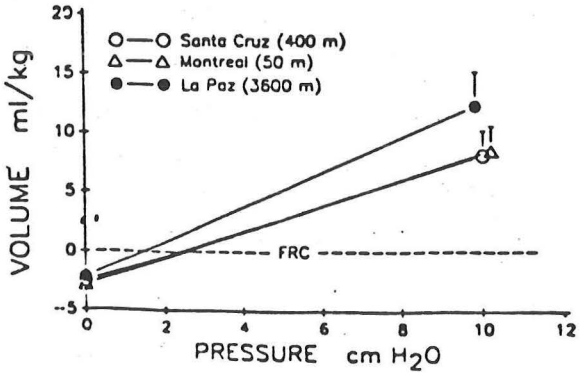


Longitudinal studies in humans are difficult and potentially confounded by the added effect of aging on the effects of high altitude exposure. A cross-sectional study was done by Monge et al [50] in Peruvians residing in 2 mining cities at sea level (n=2,838) or >4,000 m (12,000 ft., n=2,892). Vital capacity is higher in the highland residents but diminishes with age at a faster rate at high altitude, which may contribute to the age-related excessive erythropoiesis at high altitude.

DeGraff, et al [53] found a higher total lung capacity and lung DLCO in young Caucasian natives at Leadville, CO (alt. 3,100 m) compared with predicted values derived from lowlanders. Both membrane diffusing capacity and pulmonary capillary blood volume are increased. The rate of loss of diffusing capacity with age is no greater than normal.



Mean pressure-volume curves are shown for Bolivia infants born in La Paz (3,600 m) and at sea level [52]. Lung volume is higher at a given transpulmonary pressure in high altitude infants, ie. compliance of the respiratory system is increased.



The meaning of the above functional measurements is unclear. Chronic hypoxia has a depressive effect on general somatic growth. In chronically hypoxic fetal rats, lung DNA and proteins are decreased and the process of alveolar septation is diminished [56-58]. These cellular changes could decrease the elastic recoil of the lung, yielding a larger lung volume at a given transpulmonary pressure. Thus the larger lung volume might reflect blunted fetal lung development at high altitude. However, most data in larger animals and in humans suggest that lung growth and development is enhanced in high altitude populations.

The question also arises as to whether differences between highlanders and lowlanders are genetic or acquired. Differences between high and low altitude populations tend to become more marked with age [59]. Race does not appear to influence these characteristics. Teenagers who are of lowland European ancestry but who are born and raised at high altitude also have larger lung volumes [60]. Numerous animal experiments have shown that lung structure and function can be modified by chronic hypoxia in a way consistent with those reported for highlanders [61-63]. These data collectively suggest that a genetic trait is probably not the primary factor governing the highlanders' pulmonary response to chronic hypoxia.

Acute Mountain Sickness

Acute mountain sickness (AMS) encompasses a wide spectrum of high altitude illnesses of which life-threatening pulmonary edema and cerebral edema are the most extreme manifestations. Less severe but more common symptoms are generally attributable to cerebral edema and include headache, anorexia, insomnia, lethargy, nausea and vomiting; these symptoms usually occur within the first 24 hours of a rapid ascent and improve over 3 to 7 days in most patients. There may be associated peripheral and visceral edema, weight gain, oliguria and proteinuria. The incidence of AMS is about 25% at 9,000 ft and 67% at 14,000 ft. The clinical picture is consistent with a state of generalized fluid retention ± altered vascular permeability. Fluid balance is altered upon ascent to high altitude. Initially there is a shift from the intravascular space into the interstitial or intracelluar space [64]. During normal acclimatization, diuresis develops and a new equilibrium is established with a decreased total body water content. Patients developing AMS fail to acclimatize normally; they tend to possess a lower ventilatory response to hypoxia and may demonstrate higher plasma levels of renin, angiotensin II, aldosterone and antidiuretic hormone (ADH). Atrial natriuretic factor (ANF) may also be higher associated with a larger right atrial diameter. A decrease in diuresis in these patients suggest that the renal action of ANF is overridden by the opposing influence of aldosterone and ADH. Upon exercise at high altitude, increases in plasma aldosterone, ADH, norepinephrine and ACTH are greater in subjects who subsequently develop AMS than in those who do not [65]. The correlation of regulatory hormone levels with altitude or with the development of AMS is variable in different studies [66] and their precise roles in the pathogenesis of AMS are still unclear.

High Altitude Pulmonary Edema and Pulmonary Hemodynamics

Rapid ascent to high altitudes above 9-10,000 ft. may result in the development of pulmonary edema. Strenuous exercise and exposure to cold are contributing factors. The clinical syndrome is well described. It usually develops in the first week of high altitude exposure, affects young healthy individuals and tends to recur on repeat exposure to altitude. Recurrent episodes of edema generally do not show the same radiographic distribution of infiltrates [67]. Except for patients with underlying pulmonary vascular disease, there are no reliable predictors as to who will develop this complication. Long-term residents at high altitude may develop "re-entry" pulmonary edema when they return to high altitude after a short stay at lower altitude [68].

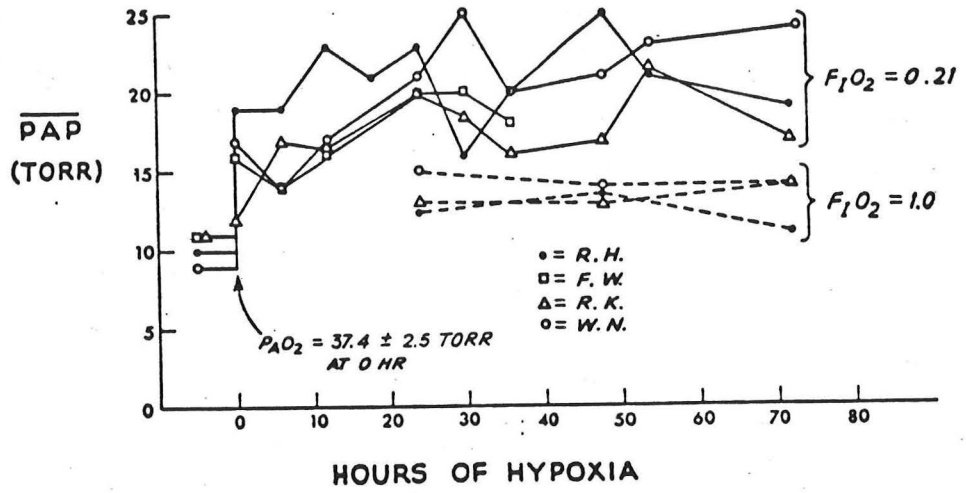
Frequency	Incidence	
Altitude	1%	General Alpine mountaineers
Speed of ascent	16%	Ascending to 14,000 ft. in 24 hr.
Individual susceptibility	60%	Susceptible subjects:
		Pulmonary vascular abnormality
		Previous history of HAPE
		"Re-entry" pulmonary edema

Features of High Altitude Pulmonary Edema

Clinical:	Dyspnea Cough Fatigue
Spirometric:	↓ FVC
Radiologic:	RV enlargement Enlarged pulmonary arteries Interstitial pulmonary congestion Patchy alveolar infiltrates
Gas exchange:	Severe hypoxemia Elevated A-a PO_2 gradient Ventilation-perfusion mismatch
Hemodynamic:	Pulmonary arterial hypertension Elevated pulmonary vascular resistance Normal to low pulmonary capillary wedge pressure

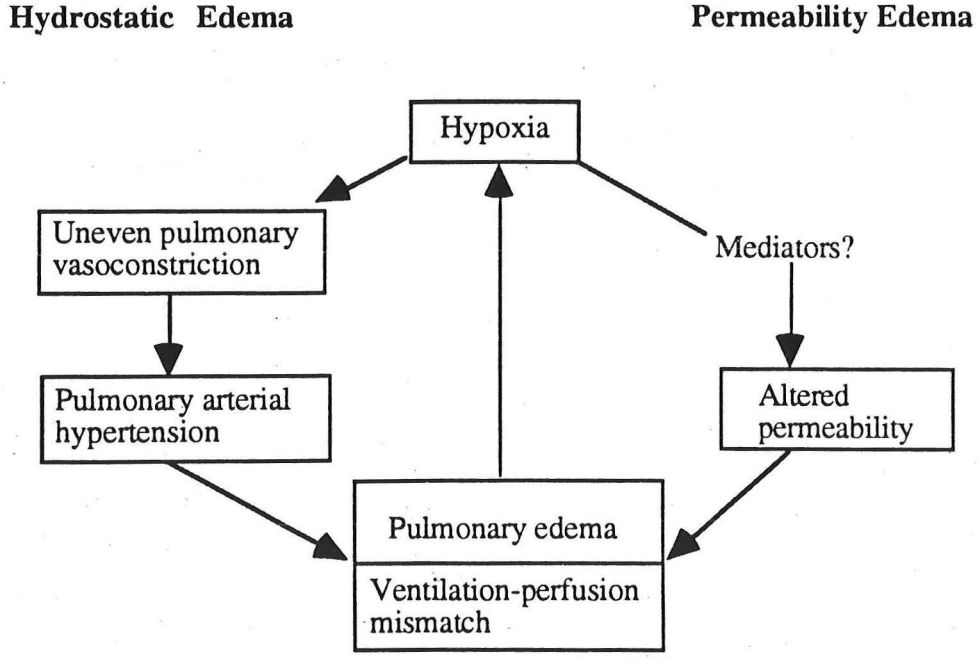
The incidence of mild or subclinical HAPE is underestimated. In Operation Everest II, 8 healthy subjects 21-31 yrs of age were taken to a simulated altitude of 8,844 m (29,000 ft) over 40 days. Two subjects dropped out from the study after developing symptoms of confusion, hypotension and brief loss of consciousness. The other 6 subjects all had restrictive changes on spirometry and radiological evidence of interstitial pulmonary

edema when compared with baseline data obtained at sea level [69]. Four subjects developed cough and sore throat; only one had rales on physical examination.



Mean pulmonary artery pressure increases in four resting subjects from sea level to 12,470 ft. Breathing 100% O_2 significantly reduces the pulmonary artery pressure [70].

The etiology of high altitude pulmonary edema is still controversial; there are two general mechanisms; both are probably important in the pathogenesis of this disease:

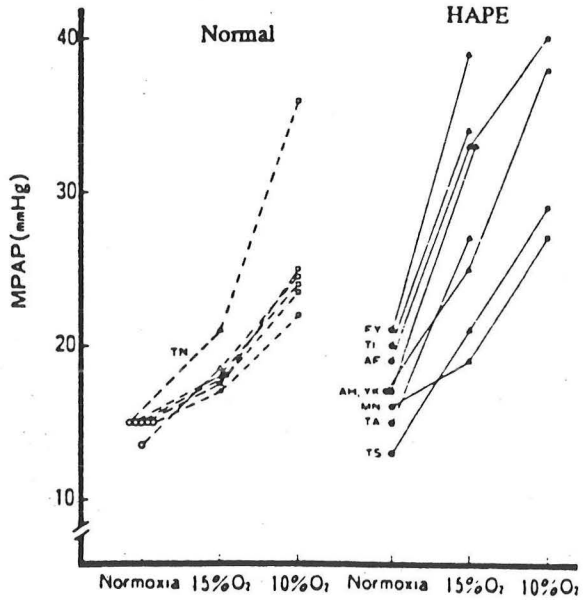


1. Hydrostatic pulmonary edema Hypoxia induces constriction of the pulmonary vascular smooth muscle leading to an increase in pulmonary arterial pressure and pulmonary vascular resistance at high altitude [70, 71]. This response takes about 24 hours to fully develop, is mediated locally and can be blocked by calcium channel blockers such as nifedipine [72, 73]. An excessively high pulmonary artery pressure is thought to be a major factor causing HAPE in susceptible individuals. One postulated mechanism is that pulmonary vascular constriction during hypoxia is not uniform, leading to high enough capillary pressures or flows in some areas of the lung to cause either disruption of the alveolar epithelium or stretching of the alveolar pores so that large molecules leak into the alveolar space. This hypothesis is supported by several findings:

a. The matching of ventilation to perfusion deteriorates upon exercise at high altitude with the development of areas of shunt and very low ventilation-perfusion ratios, suggesting that pulmonary vasoconstriction is uneven and some alveoli are more hypoxic than others [39, 41]. The arteriolar or capillary pressure in the more hypoxia regions may be considerably higher than in other regions. Mean pulmonary artery pressure may reach >50 mmHg during heavy exercise at an altitude of 8,844 m [71]. A patent foramen ovale may develop under these high pressures, providing a pathway for intracardiac right to left shunting and exacerbation of the hypoxemia [74].

b. Experimentally-induced hydrostatic pulmonary hypertension in animals results in disruption of the alveolar-capillary endothelium leading to fluid leakage into the interstitium [75-77].

c. Upon exposure to hypoxia, susceptible children in Leadville, CO. who had recovered from one episode of HAPE had greater mean pulmonary artery pressures than the non-susceptible children, implicating an increased pulmonary vasoreactivity to hypoxia in the pathogenesis of HAPE [78]. Similar results have been shown in adults [79].



From Yagi et al [79]

d. Patients with a restricted pulmonary vascular bed are more susceptible to high altitude pulmonary edema and may develop it at lower altitudes than in normal subjects. Hackett et al reported 4 patients with congenital absence of the right pulmonary artery [80]; all suffered from HAPE at altitudes of 2,000 to 3,000 m. Pulmonary edema occurred in the left lung which received the entire cardiac output but it did not develop in the right lung. Nakagawa et al [81] reported a patient who developed HAPE in the Japan Alps (2,900 m) associated with thromboembolism of the left upper lobe pulmonary artery; his pulmonary artery pressure was 56 mmHg. Torrington [82] described an association of HAPE occurring at a modest altitude of 2,300 m with right pulmonary artery occlusion from previously undiagnosed granulomatous mediastinitis.

2. Permeability pulmonary edema Hypoxia may alter alveolar-capillary membrane permeability either through an intrinsic action or through the local release of chemotactic and vasoactive mediators. This hypothesis is supported by the following:

a. Hemodynamic measurements consistently show a normal pulmonary capillary wedge pressure in the presence of pulmonary edema. Lung scans in patients with HAPE show decreased perfusion in areas of radiologic infiltrates [83].

b. The edema fluid is highly proteinaceous and cellular with predominantly alveolar macrophages. Its protein content is higher than in patients with adult respiratory distress syndrome [84, 85]. Neutrophil count is also increased in lavage fluid. Complement fragments, thromboxane B_2 and leukotriene B_4 are found in the fluid, although it is unclear whether they are the cause or result of the fluid leak.

c. Some investigators have reported an increased pulmonary lymph flow and microvascular fluid filtration in dogs exposed to hypoxia [86, 87], although others found no such increase [88, 89] in sheep exposed to hypoxia. Rats exposed to an altitude of 14,500 ft (P_B 450 torr) for 24 to 48 hours developed significant transvascular protein leak in the lung, measured by radiolabeled ^{125}I-albumin corrected for lung blood content with ^{51}Cr-tagged red blood cells [90]. This protein leak is further exaggerated if the animal has been adrenalectomized, suggesting that endogenous glucocorticoids play a role in modulating the permeability of the alveolar membrane. These data reflect species differences in the propensity to develop pulmonary edema and the mechanisms involved.

d. Patients with HAPE show relative thrombocytopenia and prolonged prothrombin time [83]. Genton et al [91] studied young calves at altitude and noted a lower platelet count, platelet half-life, a longer prothrombin time, shorter thromboplastin time, and lower fibrinogen and fibrinogen half-life. Gray, et al [92] using ^{51}Cr-labeled platelets, found evidence of sequestration of platelets in the lungs in rabbits exposed rapidly to 6,100 m. Postmortem findings in patients with HAPE show numerous scattered microvascular thrombi [93, 94]. Thus altered platelet function may play a role in initiating the changes that lead to increased vascular permeability.

e. The frequent association of pulmonary edema with cerebral edema and subcutaneous edema suggests a global fluid imbalance and increase in vascular permeability [95].

There appears to be no consistent relationship between the strength of hypoxic ventilatory response or the degree of hypoxemia in a particular individual and the development of pulmonary edema [96, 97]. High altitude pulmonary edema can occur in susceptible individuals despite the presence of a normal or high ventilatory response to hypoxia [97].

Treatment of Acute Mountain Sickness

Descent

Mild symptoms
Rest
Acetaminophen, Ibuprofen
Acetazolamide 250 mg b.i.d.

Moderate symptoms
Rest
Dexamethasone 4 mg q6h for 1-3 days, taper over 5 days
Acetazolamide 250-500 mg b.i.d. to t.i.d.

Severe symptoms
Oxygen
Dexamethasone 8 mg followed by 4 mg q6h p.o. or i.m.
Acetazolamide up to 1.5 g daily

Acetazolamide effectively relieves symptoms of AMS. **Dexamethasone** is also effective in reducing AMS symptoms; this treatment over 2 days does not alter fluid balance or plasma volume changes, but is associated with suppressed cortisol secretion [98]. Dexamethasone does not improve objective physiologic abnormalities related to high altitude exposure and is associated with mild hyperglycemia in all subjects [99]. Both drugs are effective in treating symptoms of established AMS. Acetazolamide is the preferred agent because it is associated with increased ventilation, improved oxygenation and prevention of periodic breathing [100, 101] and its side effects are relatively minor. Both drugs may be used together in severe cases.

Action of Acetazolamide

Carbonic anhydrase inhibitor

Diuresis

Urinary loss of bicarbonate, sodium and potassium

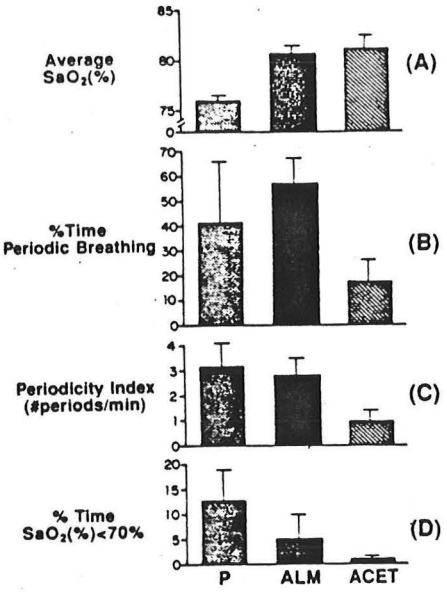
Metabolic acidosis

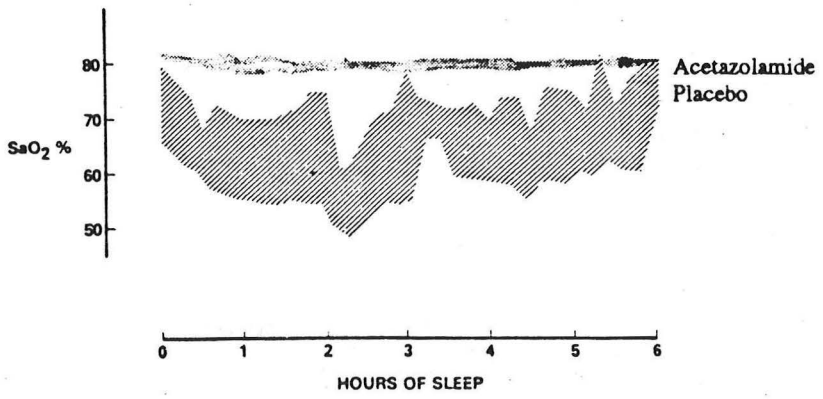
Compensatory hyperventilation

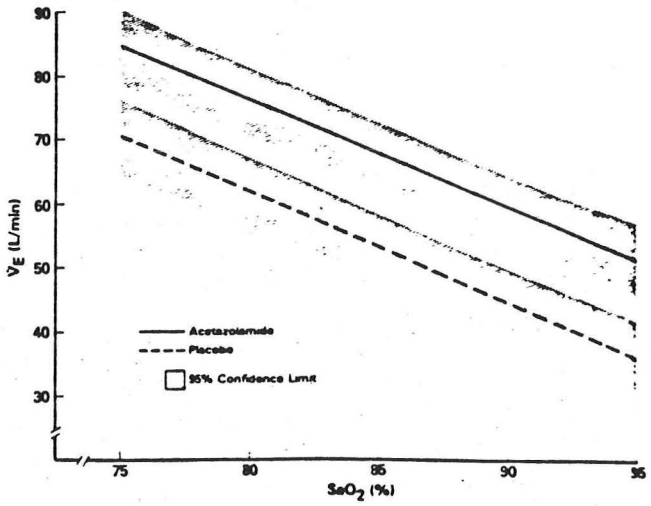
Improvement in periodic breathing

Improvement in oxygenation

Acetazolamide (ACET) is superior to placebo (P) and other respiratory stimulants such as almitrine (ALM) in suppressing periodic breathing and maintaining oxygen saturation during sleep at high altitude [102].







From Sutton et al [103]

Efficacy of Acetazolamide in Reducing the Frequency (%) of Symptoms During Rapid Ascent to 3,900 m (12,800 ft) [104, 105]

Headache	100	→	65
GI symptoms	75	→	48
Insomnia	78	→	40
AMS	67	→	17

Side Effects of Acetazolamide

Paresthesias

GI upset

Somnolence

Altered taste for carbonated beverages

Treatment of High Altitude Pulmonary Edema

Descent

Oxygen

Positive pressure breathing

Dexamethasone

Nifedipine

Acetazolamide

Compression chamber

Mortality of HAPE ranges between 0 to 50% depending on the speed of diagnosis, availability of medical facilities and means of transportation to lower altitudes. **Descent** is the definitive treatment and should be effected as soon as possible. Descending by as little as 1,000 ft often leads to dramatic clinical improvement. **Oxygen** administration is effective if given early in the course of illness [106]. Once established, however, the syndrome may not easily reverse with oxygen. **Expiratory positive airway pressure** (EPAP) up to 10 cmH_2O improves oxygenation in patients with HAPE; tidal volume is increased and respiratory rate decreased without changing minute ventilation [107]. It may be an effective temporizing measure in patients who cannot immediately descent to lower altitudes.

Dexamethasone 8 mg initially and then 4 mg q6h p.o. has been found in placebo-controlled trials to effectively reduce symptoms of moderate to severe mountain sickness and cerebral edema [108, 99]; it may be used in HAPE but the efficacy has not been established. **Acetazolamide,** up to 1.5 g per day, may also alleviate the symptoms by

stimulating ventilation and inducing diuresis but again its efficacy in established HAPE has not been well studied. Furosemide has never been proven to improve oxygenation in this syndrome and may be associated with pulmonary embolism, hemodynamic deterioration and worsening cerebral edema [109].

Nifedipine (10 mg sublingually + 20 mg slow release p.o. immediately followed by 20 mg slow release p.o. q6h) effectively lowered pulmonary hypertension, improved performance and oxygenation over 36 hours in mountaineers who developed HAPE in the Swiss Alps at 4,559 m [72]. It also led to regression of radiologic features of pulmonary interstitial edema in these patients. Effective ventilation was not altered. Nifedipine works by blocking calcium influx in pulmonary arterial smooth muscle, leading to reductions in pulmonary vascular pressure, fluid extravasation, the afterload of the right ventricle, and the hypoxia that precipitated the syndrome. However, nifedipine also blocks calcium channels in other cells. Calcium is a necessary messenger in many steps in inflammation, including the activation of phospholipase A2, the initiating step in eicosanoid synthesis. Therefore a second mechanism of nifedipine action could be to blunt the inflammatory response associated with HAPE and thereby reducing permeability of the membrane [110].

Prevention of Acute Mountain Sickness

Common sense

Recognize variation in individual susceptibility

Avoid alcohol, sedatives

Avoid excessive exertion on first day

Slow ascent

2-5 days at 2,000 m (6-7,000 ft)

Above 3,000 m (10,000 ft) ascend 300 m (1,000 ft) per day

Acetazolamide

250-500 mg q.h.s. starting day before ascent

Continue for 3-5 days

(Nifedipine)

20 mg q.d. for 2 days before ascent

20 mg q8h starting on day of ascent for 3 days

(Dexamethasone)

2-4 mg q6h starting on day of ascent

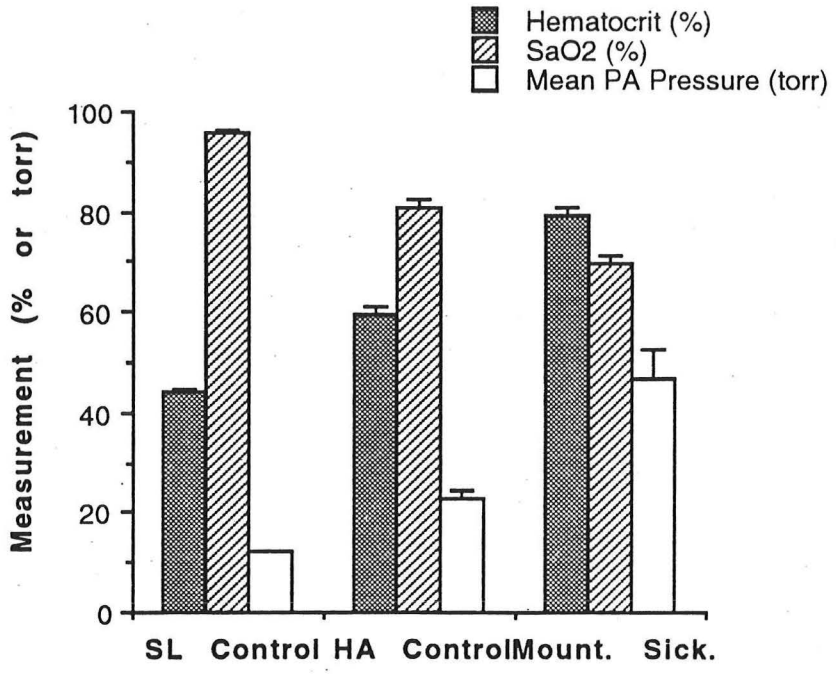
Continue for 3 days, taper over 5 days

Both AMS and HAPE can be effectively prevented by **acetazolamide** [101]. **Nifedipine** is a new prophylactic agent for HAPE and has not been clearly shown to be beneficial in AMS. Bärtsch et al [73], in a double-blind, randomized trial, assigned 21 mountaineers with a history of radiographically documented HAPE to receive either nifedipine or placebo while ascending rapidly from 1,130 m to 4,559 m. Subjects stayed at this altitude for 3 days. Seven of 11 subjects receiving placebo and 1 or 10 subjects receiving nifedipine developed HAPE. Those receiving nifedipine had significantly lower pulmonary artery pressure, alveolar-arterial O_2 tension gradient and symptom scores. However, it should be started before ascent to detect potential side effects, ie. hypotension. It is indicated only in subjects who are at high risk of developing HAPE. **Dexamethasone** has been found to be superior to acetazolamide in preventing AMS. Mild hyperglycemia is common but serious side effects are rare; however, some degree of adrenal suppression does occur and symptoms compatible with recurrent AMS or adrenal insufficiency have been observed after abrupt discontinuation of the drug [111]. For this reason it is not routinely recommended for prophylaxis.

Chronic Mountain Sickness

Chronic mountain sickness (CMS) was originally described in 1928 as a syndrome occurring in indigenous Quechua Indian residents of high altitude in the Andes [112, 113]. It was characterized by exaggerated features of normal responses to life-long residence at high altitude, i.e. accentuation of polycythemia, cyanosis, pulmonary hypertension, large chest, clubbed fingers, and right ventricular strain. Right heart failure often supervened. The term "la enfermedad de los Andes" was applied to the syndrome by the Peruvian physician, Carlos Monge, who first described it. Now it is most often referred to as Monge's disease in the medical literature or as Soroche. Penaloza [114] described the characteristic physiologic features of the disease in patients native to Cerro de Pasco, Peru (14,200 ft.) and in healthy residents of Cerro de Pasco and of Lima which is at sea level (Figure below). Patients were of mixed Indian and European descent, indicating that the disease is not peculiar to the Quechua Indians.

It was originally thought to be a disease peculiar to life-long residents of the Andes [115]. However in 1958 a case was reported in a 24 year old native of Fairplay, Colorado at an altitude of 9,580 feet [116]. This patient had marked polycythemia (Hematocrit 76%) associated with easy fatiguability and shortness of breath and significant arterial oxygen desaturation in the face of a normal arterial P_{CO_2}; EKG showed right ventricular strain and cardiac catheterization revealed pulmonary hypertension. Symptoms and findings subsided on moving to Los Angeles although mild pulmonary hypertension and mild arterial oxygen desaturation persisted. Based on this patient it was proposed that at least "some cases of mountain sickness result from intrinsic lung disease, too mild to cause signs or symptoms at sea level". It was soon recognized that these patients usually had impaired ventilatory drive as a primary disturbance. Severinghaus et al. [117] described a marked decline in the ventilatory response to hypoxia in long-term residents of high altitude which was exaggerated in those who developed chronic mountain sickness. Weil et al also described a progressive loss of ventilatory drive to hypoxia in long term residents of high altitude in the Rocky Mountains [24] which correlated with the length of stay at high altitude. Ergueta et al. [118] reported studies on 20 native residents of La Paz, Bolivia (12,010 feet) with chronic mountain sickness in comparison with healthy native controls. Their findings also suggest primary hypoventilation as the principle derangement.



Hematocrit (Hct), arterial oxygen saturations (SaO_2), and Pulmonary Artery (PA) Pressure in patients with chronic mountain sickness in Cerro de Pasco, Peru, in healthy residents at 14,200 ft. (HA Control) and in healthy residents of Lima at sea level (SL Controls). From Penaloza [114].

Characteristics of Chronic Mountain Sickness in La Paz, Bolivia (12,010 ft.)

	Healthy Natives	CMS
Number	14	20
Mean age	51	24
Hematocrit (%)	50.3	72.1*
Total blood vol. (L)	5.72	6.91
Pa_{CO_2} (torr)	34.7	43.5*
Pa_{O_2} (torr)	56.7	47.9*
(A-a)P_{O_2} (torr)	-0.4	-1.3
Sa_{O_2} (%)	89.7	82.8*
Mean PA Pressure (torr)	22.9	51.5*

* Significantly different from controls ($p<.05$). From [118].

CMS has been recognized in Caucasian residents of Leadville, Colorado [119, 120] at an altitude of 10,200 ft. Kryger and his associates attributed the impaired ventilatory response to hypoxia to either of two potential mechanisms, an impaired chemical drive to breathe or an impaired end-organ response (i.e., mechanical impairment or gas exchange impairment of the lung due to mild disease). Patients were divided into two groups, ***Group 1:*** in whom lungs were normal but there was an **altered ventilatory drive** and ***Group 2*** in whom ventilatory drive was normal but **lungs were abnormal** causing impaired alveolar-capillary gas exchange. Seven of the patients in **Group 2** had mild chronic obstructive airways disease and 3 had mild restrictive lung disease; inefficient gas exchange was apparent from a significantly higher alveolar-arterial oxygen tension difference [(A-a)P_{O2}] in patients of **Group 2** than in controls or patients of **Group 1**.

Characteristics of Chronic Polycythemia in Leadville, Colorado (10,200 ft.)

		Patients	
	Controls	**Group 1** (Normal Lungs)	**Group 2** (Abnormal Lungs)
Number	10	8	10
Mean age	49	46	56
Years at HA	41	31	45
Hematocrit (torr)	47.9	59.3*	62.0*
Pa_{CO2} (torr)	30.9	33.5*	33.2*
Pa_{O2} (torr)	54	47*	41*
(A-a)P_{O2} (torr)	8	10	18*
Sa_{O2} (%)	91.6	86.2*	81.0*

* Significantly different from controls ($p<.05$). From [119].

The cause of deranged ventilatory control is not understood. All long term residents of high altitude tend to develop a progressive decline in ventilatory response to hypoxia, presumably due to impaired carotid body function, but this decline does not clearly correlate with the development of chronic mountain sickness. Some other yet unknown factor exists. Both **Groups 1 and 2** respond to methoxyprogesterone acetate (MPA) which effectively increases the ventilatory response to hypoxia but not to hypercapnia.

Response to MPA in Patients with Chronic Mountain Sickness

	Normal Lungs		Abnormal Lungs	
	Control	MPA	Control	MPA
Hematocrit (%)	59.0	49.9*	61.4	54.5*
Pa_{CO2} (torr)	33.4	29.9*	32.4	27.5*
Pa_{O2} (torr)	46.8	49.7*	41.5	44.9*
Sa_{O2} (%)	85.9	91.2*	81.8	87.9*

* Significantly different from controls ($p<.05$). From [121].

In summary, chronic mountain sickness develops in long term residents of high altitude and apparently reflects a loss of ventilatory acclimatization. A low or absent ventilatory response to hypoxia, excessive hypoxemia, secondary polycythemia, pulmonary hypertension and cor pulmonale are the hallmarks of this disease. The definitive treatment is descent to lower altitudes where rapid abatement often occurs in symptoms, physical findings and laboratory abnormalities. Medroxyprogesterone and other respiratory stimulants may be used in patients who cannot move to lower altitudes for various reasons.

Air Travel and Patients with Cardiopulmonary Disease

The incidence of emergency medical problems developing in patients during commercial flights is low, about 0.003 %. Of 2,415 such incidents the breakdown into categories is as follows [41]:

	Number	Percentage
Cardiovascular	501	20.7
Neurologic	433	17.9
Gastrointestinal	265	11.0
Pulmonary	199	8.2
Trauma	82	3.4
Other	652	25.9
In flight deaths	21	0.9

Commercial aircraft cruise at altitudes ranging between 22,000 and 44,000 feet; cabin pressure is maintained at levels equivalent to 5,000-8,000 feet [41]. Normal inspired P_{O2} after humidification at sea level is 149 mm Hg, but during an airline flight inspired P_{O2} will decrease 25 to 40 mm Hg below that at sea level. In a normal individual acutely exposed to an altitude of 8,000 feet, arterial oxygen tension will fall to about 56 mm Hg and arterial oxygen saturation to about 88%; symptoms of acute mountain sickness seldom occur under these sedentary conditions. In general patients with stable cardiac disease or chronic anemia tolerate the stress of altitude exposure better than patients with respiratory disease because of their normal ventilatory reserve, ie. they could increase O_2 uptake and maintain oxygenation by hyperventilation. Patients with chronic obstructive lung disease (COPD) have a lower ventilatory reserve and cannot increase their ventilation to the same extent as in normal subjects in response to a hypoxic challenge. Their low arterial PO_2 at ground level may lie on the steep portion of the oxyhemoglobin dissociation curve so that arterial O_2 saturation will drop precipitously at higher elevations. The change in arterial oxygen tension expected in patients with COPD during a commercial airline flight at an altitude equivalent of 8,000 feet have been measured and can be approximated from measurements of PaO_2 and FEV_1 at sea level by the following empirical equation [122]:

$$Pa_{O2}\text{ (during flight)} = 0.453\ Pa_{O2}\text{ (sea level)} + 0.386\ FEV_1\ (\%\ \text{Pred}) + 2.44.$$

Thus a patient with moderate COPD having a Pa_{O2} of 65 mm Hg and an FEV_1 of 40% of normal at sea level would have an inflight PaO_2 of about 47 mm Hg and an arterial oxygen saturation of about 82%. Light exertion could drop this another 5 to 10 mm Hg

and reduce the arterial oxygen saturation further to 71-78%. Such impairment in arterial oxygenation is equivalent to that seen in normal subjects at altitudes of 14,000 feet where a high incidence of acute mountain sickness can be expected in active individuals. Most patients with moderate COPD, $PaO_2 \geq 60$ mm Hg and $FEV_1 \geq 40\%$ of normal, will tolerate short term adaptation to the moderate altitude equivalents of commercial air flights [123]. For those patients requiring oxygen at sea level or traveling to higher altitudes overland during which oxygen supplements are required to maintain sea level arterial gas tensions, inspired oxygen concentrations (FIO_2) need to be increased according to the barometric pressure at a given altitude (P_B) [44]:

$$FIO_2 \text{ (required at altitude)} = FIO_2 \text{ (required at sea level)} \times \frac{760}{P_B \text{ (at altitude)}}$$

[41]

For commercial air flights, the following approximation is useful:

FIO_2 (sea level) x 760 = FIO_2 (8,000 feet) x 565 i.e.,

FIO_2 (in flight) = FIO_2 (sea level) x 1.34 or

Nasal cannula flow (in flight) = Nasal cannula flow (sea level) x 1.34

Commercial airlines will supply oxygen on request for in flight use for patients requiring oxygen. Cost is generally between $40 to $150 depending upon the number of tanks required. Mode of administration, whether by nasal cannula or mask depends upon the carrier. A prescription is generally required from a physician. Oxygen-dependent patients should avoid sedatives, carbonated beverages, high carbohydrate meals and alcoholic beverages during flight.

Effects of High Altitude on Patients With Lung Disease

Short-term adaptation to moderate altitude

Graham and Houston [123] studied the effects of 4 days acclimatization to an altitude of 6,315 ft in 8 patients with moderate chronic obstructive lung disease (COPD). Mean FEV_1 was 1.27 L (41% of predicted) with an average FEV_1/FVC ratio of 43 %. Blood gases during rest and exercise at sea level and after 4 days of acclimatization are shown below.

	At Sea Level		At 6,315 feet	
	Rest	Exercise	Rest	Exercise
Pa_{CO_2} (torr)	37.6	38.8	32.9*	33.7*
pH	7.42	7.39	7.45	7.43*
Pa_{O_2} (torr)	66.0	63.0	54.0*	46.6*
A-a DO_2 (torr)	35.4	37.6	24.9*	28.9*

* $p<0.05$ compared to sea level data

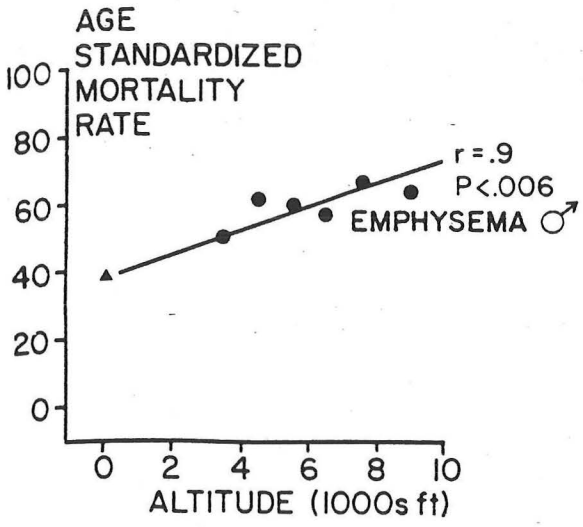
After 4 days significant compensatory hyperventilation was noted in response to the hypoxia and arterial oxygen tension had risen from an initial level of 51 torr at rest to 54 torr. Exercise caused a further drop in Pa_{O_2} of about 8 torr, equivalent to a fall in oxygen saturation from 87% at rest to 81% during exercise. Blood gases seen in these patients were equivalent to those seen in normal individuals at altitudes between 14,000 and 15,000 feet where acute mountain sickness is common. Yet these patients did not develop signs and symptoms of acute mountain sickness and seemed to tolerate normal activities well, perhaps because their chronic hypoxia had provided some degree of pre-acclimatization.

Thus patients with moderate COPD who do not have CO_2 retention and have arterial oxygen tensions above 60 torr at sea level seem to tolerate short term stays at moderate altitudes between 5,000 and 8,000 feet without supplemental oxygen and without apparent propensity to develop acute mountain sickness.

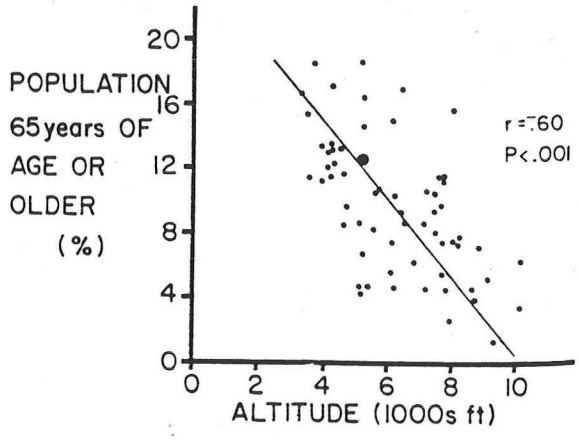
Long term effects of high altitude on patients with lung disease

In contrast to the apparent tolerance to short term exposure, ample documentation exists that long-term moderate altitude exposure between 4,000 and 10,000 feet is detrimental to patients with chronic lung disease. It was first pointed out by Renzetti that patients with similar degrees of chronic obstructive lung disease (COPD) had a higher mortality from cor pulmonale at altitudes between 4,000 and 9,000 feet than at lower altitudes in Utah and New Mexico [124]. Although CO_2 retention tended to be less in the high altitude patients, arterial oxygen saturation was significantly lower and polycythemia accentuated. Patients with lung disease too mild to cause significant symptomatology at sea level may be at risk for developing all the features of chronic mountain sickness at high altitude particularly if long-term residence there has depressed normal chemoreceptor drive to ventilation [116, 119]. Age standardized mortality rate from emphysema in Colorado shows a significant positive correlation with altitude ($r = 0.9$)

between sea level and 10,000 feet [125]. Additionally a decline in the proportion of elderly persons at high compared to low altitude has been documented by census figures in Colorado [126]. This is not just a consequence of increased mortality. Colorado census data also shows selective out-migration from high to low altitude primarily for health reasons, 81% related to heart or lung disease [126].



Age standardized mortality rates calculated for altitude groups in Colorado increase with altitude and in comparison with national rates (triangle) for males. Rates are expressed as per 100,000 male residents older than 35 yr of age [125].



The percentage of persons ≥ 65 yr of age decreases at higher altitudes in Colorado. Data are computed for each of 63 counties in Colorado from 1975 population estimates. Denver, the most populous, is shown as the largest dot [126].

In conclusion, moderate altitudes > 4,000 feet increase the morbidity and mortality in patients with chronic lung disease. At altitudes over 9,000 feet even mild lung disease in long-term residents may increase the risk of chronic mountain sickness if, because of long residence at high altitude, chemoreceptor ventilatory drive becomes significantly depressed. Patients recognize the differences in symptomatology they experience between high and low altitudes and tend to move to lower altitudes on their own volition.

Summary

The human being is not as well adjusted to the hypoxia of high altitude as some animals (eg. yak, llama) and cannot permanently live at altitudes above about 14,000 ft. The major pathophysiologic effects of high altitude exposure are derangements in ventilatory control and gas exchange, leading to secondary changes in fluid balance and vascular permeability. Normal acclimatization involves adjustments of the respiratory center, erythropoisis and diuresis. Complications of high altitude exposure can generally be avoided by a slow ascent. Acetazolamide is the most commonly used drug in preventing

mountain sickness. Mild high altitude pulmonary edema is more common than generally recognized. Pulmonary edema developing at altitudes <10,000 ft. could signal the presence of underlying pulmonary vascular disease. Long-term residence at high altitude is associated with progressive attenuation of ventilatory acclimatization and may lead to the development of chronic mountain sickness, particularly in patients with mild lung disease. High altitude residence increases the morbidity and mortality of patients with existing lung disease. Patients on chronic supplemental oxygen therapy should have their flow rates adjusted when travelling to high altitudes.

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