



Physiology of High-Altitude Acclimatization: Review Article

Bahaeldean E. Elawad

Department of Physiology, Faculty of Medicine,
University of Umm-ALqura, Holy Makkah, King Saudi Arabia

ABSTRACT

As the barometric pressure decreases exponentially within the troposphere, the partial pressure of oxygen decreases proportionally in ambient air, inspired air, alveolar air, and arterial blood. The primary physiologic challenge with altitude is reduced partial pressure of oxygen (hypobaric hypoxia). Physiologic adaptation to decreasing partial pressure of oxygen in the high-altitude environment is known as acclimatization. It is a complex, not yet fully understood, mechanism to preserve cell function despite reduced oxygen supply to the tissues. Chronic adaptation includes improving oxygen transport capacity and restoring oxygen delivery to the tissues. Of the three successful patterns of adaptation to chronic high-altitude hypoxia; the Amharas have the legend one. Normal partial pressure of oxygen in arterial blood despite inevitable hypobaric reduction of partial pressure of oxygen in inspired air is a puzzler and big challenge to respiratory physiology. Amharas have elevated nitric oxide which suggests the possibility of adaptation via vasodilatation, which would increase oxygen supply to metabolic tissues. Left shift of ODC under influence of nitric oxide seems to be an integral component of Amharic pattern of adaptation. The mechanism of which is not known. It could be hypothesized that native Amhara highlanders have increased, pulmonary capillary transit times; finite reaction of hemoglobin with oxygen; and oxygen-carrying capacity of hemoglobin than other high-altitude populations. Further research is warranted to explore the physiologic mechanism by which Amhara highlanders maintain normal PaO₂ despite hypobaric hypoxia. This is a potential breakthrough in management of critically ill hypoxic patients at intensive care settings.

Keywords: Barometric pressure, High altitude, Partial pressure of oxygen, Hyperventilation, red blood cell mass, hypoxic pulmonary vasoconstriction, oxygen-hemoglobin dissociation curve, oxygen-carrying capacity of hemoglobin, Finite reaction of hemoglobin with oxygen.

Earth is surrounded by an atmosphere, sea of air, several hundred miles high which is retained by earth's gravity. It is composed of six layers. The lowest layer is the troposphere which envelops the earth's entire surface up to a height of approximately 10.000 meters (m) {33.000 feet (ft)} (1).

The atmosphere contains the earth's air, which is a mixture of gases. Nitrogen and oxygen are by far its most abundant gases; all other gases together make up less than 1% of the air. Atmospheric air has a composition of 79.03% nitrogen, 20.93% oxygen, and 0.04% carbon dioxide and other gases. The total dry (nonvapor) atmospheric (barometric) pressure (P_B) induced by these gases, at sea level, is 760 mm Hg (2).

The concentration of these gases in atmosphere remains constant, at least throughout the breathable atmosphere (3).

Within troposphere, the (P_B) falls exponentially, as altitude (vertical height above sea level) increases. As the P_B decreases, the partial pressure of oxygen (PO_2) decreases proportionally in ambient air, inspired air, alveolar air, and arterial blood (4).

According to Dalton's law of gases, the partial pressure exerted by an individual gas in a mixture of gases will be equal to the fractional concentration of this particular gas multiplied by the total pressure of gas mixture (5). So, PO_2 is approximately 160 mm Hg in ambient "dry air", at sea level.

High altitude is generally considered to be an altitude higher than 1500 m above sea level. It is further classified as:

- High (1.500-3.500 m) (4.950-11.550 ft): high-altitude sickness usually occurs during a rapid ascent above 2.500 m (8250 ft).
- Very high (3.500-5.500 m) (11.550-18.150 ft): severe high-altitude sickness most commonly occurs at this altitude, which requires a period of adaptation and where climbing can be dangerous.
- Extreme (5.500-8.850 m) (18.150-29.200 ft): At these altitudes, there is progressive deterioration of physiological functions that quickly exceeds the biological adaptability processes. Excessive rapid ascent almost always precipitates severe disease; with severe hypoxia and hypocapnia (6).

At 4550 m (15.000 ft) height, P_B is 640 mm Hg, and PO_2 in dry air is 134 mm Hg. At 5.500 m (19.000 ft) height (Everest Base Camp), the highest altitude at which people have settled, the P_B and PO_2 are half of sea level values, 380 and 80 mm Hg respectively. At, summit of Mount Everest, 8550 m (29.000 feet), the highest point above sea level on earth's surface, P_B is 253 mm Hg and PO_2 is 53 mm Hg. At 19.200 m (63.000 ft), P_B is 47 mm Hg and PO_2 in dry air is 10 mm Hg, which is incompatible with life (7).

Therefore, the primary physiologic challenge with altitude is reduced PO_2 (hypobaric hypoxia); other environmental stressors include low temperature and humidity and increased ultraviolet radiation.

Classic oxygen cascade is a physiological description of the step-wise decrease in PO_2 from the atmosphere to mitochondria.

The PO_2 in dry (nonvapor) air at sea level is 160 mm Hg.

Since airways are open to the atmosphere, average airway pressure also equals 760 mm Hg. However, water vapor is added to inspired air for warming and humidification. Water vapor pressure (P_{H_2O}) in humans is 47 mm Hg at normal core body temperature. This addition results in reduction of dry (nonvapor) P_B by an equal amount. Therefore, the partial pressure of oxygen of inspired air (PIO_2) will be equal to fractional concentration of oxygen in inspired air (FIO_2) multiplied by (P_B minus P_{H_2O}), which is approximately 150 mm Hg.

Partial pressure of oxygen in alveoli (P_{AO_2}) is determined by the balance between removal of oxygen from alveolar gas into pulmonary capillary, and replenishment of oxygen from atmosphere into alveoli. Inspired air does not contain carbon dioxide. Carbon dioxide in alveoli comes from pulmonary capillaries. Partial pressure of carbon dioxide in the alveoli (P_{ACO_2}) is 40 mm Hg which is the result of normal alveolar ventilation. Alveolar ventilation is the volume of air that reaches the alveolar-capillary membrane and participates in gas exchange process. P_{AO_2} is proportional with addition of carbon dioxide into alveoli (8).

At rest, the ratio between carbon dioxide produced ($\dot{V}_{CO_2}$) (200 ml/min) and oxygen consumed ($\dot{V}_{O_2}$) (250 ml/min) is known as respiratory quotient (RQ) or respiratory exchange ratio; which is approximately 0.8. Thus, as air moves from the trachea to the alveoli, PO_2 will fall 1.2 mm Hg for every 1 mm Hg increase in partial pressure of carbon dioxide in arterial blood (P_aCO_2). If the PIO_2 is 150 mm Hg and the P_aCO_2 is 40 mm Hg, this will yield a P_{AO_2} of 102 mm Hg (9). Such relationship is expressed by alveolar gas equation which estimates the P_{AO_2} (10). It is the most important physiologic equation in respiratory medicine:

$$P_{AO_2} = (P_B - P_{H_2O}) FIO_2 - P_aCO_2/RQ$$

Over 140 million people in the world live permanently at an altitude greater than 2500 m (8250ft) (11).

Lowlanders can survive and live permanently at an altitude of up to 4900 m (16170 ft), whereas native highlanders can reside at a maximum altitude of 5800-6000 m (19140-19800 ft) (12).

Physiologic adaptation to decreasing PO_2 in the high-altitude environment is known as acclimatization. It is a complex, not yet fully understood, mechanism to minimize hypoxemia and preserve cell function, despite reduced oxygen supply to the tissues. It involves roughly the whole of the body, with limits that vary with individuals and different ethnicities (13).

Acute adaptation at high altitude includes increased ventilation (14), changes in metabolism (15), protection against hypoxia-induced cell death (16), and vasodilatation (17).

Chronic adaptation includes restoring oxygen delivery to the tissues. That is to say, improving oxygen transport capacity by increasing red blood cell mass and hemoglobin concentration, remodeling of existing vessels as well as formation of new blood vessels "angiogenesis" (18). These adaptations probably occur at the cellular level and are mediated by transcription factors; especially activated under hypoxic conditions. The most important of which is hypoxia-inducible factor (HIF)-1, an oxygen sensitive transcription factor (19).

HYPERVENTILATION

At high altitude the uptake of a given amount of oxygen requires a higher level of pulmonary ventilation than at sea level due to the lower PO_2 . Pulmonary ventilation is defined as the volume of gas that is inspired or expired each minute regardless, of its participation in process of gas exchange at alveolar-capillary membrane. Pulmonary ventilation is the product of tidal volume and respiratory frequency. Tidal volume is the volume of gas that is inspired or expired each breath cycle.

Hyperventilation is “traditionally” the first efficient line of defense against hypoxemia (14). It should be emphasized that, it is the “hyper-alveolar ventilation” which determines the P_{aCO_2} and consequently the P_{aO_2} . Hyper-alveolar ventilation is the portion of pulmonary ventilation that reaches the alveolar-capillary membrane and participates in gas exchange process. The exchange of carbon dioxide and oxygen across alveolar-capillary membrane is the central mechanism of respiratory physiology. The efficiency of this central mechanism is “only” determined by the difference between P_{aO_2} and partial pressure of oxygen in arterial blood (P_{aO_2}). This difference is referred to as A-a difference (20).

Within minutes of climbing above 1500 m (4950 ft), both tidal volume and respiratory frequency increase in proportional to the degree of hypoxemia detected by peripheral carotid body chemoreceptors (14).

This Physiological response, known as hypoxic ventilatory response (HVR) which is responsible for a rapid decrease in the P_{aCO_2} and a proportional increase in P_{aO_2} .

Hyperventilation is a critical response to acute and chronic hypoxia. This is appreciated by considering the summit of Mount of Everest, where P_B is 253 mm Hg and PIO_2 is only 43 mm Hg. Assuming a normal respiratory quotient of 0.8, the alveolar gas equation yields a resting P_{aO_2} of minus 7 mm Hg! Which of course is incompatible with life. Actual Everest summit resting P_{aO_2} and P_{aO_2} is remarkably in the region of 30-35 mm Hg while P_{aCO_2} or P_{aCO_2} is astonishingly lower, at 7-12 mm Hg (21).

However, the effectiveness of this HVR is partially diminished by consequent respiratory alkalosis, which inhibits the medullary respiratory center (22).

Correction of alkalosis by renal excretion of bicarbonate is not the primary basis for continuing increases in ventilation with altitude acclimatization. Ventilatory response to hypoxia occurs within seconds which is too fast to be explained by P^H changes in the blood. It is now known that hyperventilation with acute hypoxic exposure is primarily a carotid body/central chemoreceptor-mediated reaction to low P_{aO_2} (23).

Additionally, the sensitivity of peripheral and central chemoreceptors to low P_{aO_2} is raised and plays the major role in continuing ventilatory acclimatization, despite presence of respiratory alkalosis (24). Interestingly, those who experience adaptation usually respond more strongly to future hypoxia after returning to normal oxygen status compared to nonadapted subjects (25).

Carotid body is located in the bifurcation of the common carotid artery. This body is the main peripheral chemoreceptors sensitive to chemical changes in composition of arterial blood including low P_{aO_2} and hypercapnic acidic stimulation (high P_{aCO_2} and high hydrogen ion concentration) (26).

These chemoreceptors play a central role in cardiorespiratory, autonomic, and humoral responses to hypoxemia (27).

Acute hypoxemic or hypercapnic acidic stimulation of carotid body triggers reflex responses including hyperventilation (28).

The structural unit of the carotid body is the glomoid formed by chemoreceptor (type I or glomus cells), oxygen sensing elements, which are organized around the capillaries and are surrounded by cells of glial origin (type II cells) (29).

Type I cells are innervated by axons of primary sensory neurons with somata in the petrosal ganglia (PG) that project to the nucleus of the solitary tract (NTS) (30).

The most widely accepted hypothesis for stimulus transduction holds that hypoxia and hypercapnic acidic sensing occur in the type I cells and is coupled to calcium-dependent secretion of one or more excitatory transmitters that increase discharge to sensory neurons (31,32).

Despite major advances in understanding oxygen sensing process in the carotid body over the last six decades, the precise nature of molecular mechanism remains incompletely understood (33).

Furthermore, the identity of the excitatory transmitter(s) between type I cells and nerve endings of the petrosal neurons is still debated (33).

OXYGEN HEMOGLOBIN DISSOCIATION CURVE

Adequate perfusion of body tissues with oxygen and nutrients requires sufficient cardiac output, intact vascular system that transports blood to tissues and back to the heart, volume of blood that fills the vascular system, and tissues able to utilize oxygen and nutrients (34).

Oxygen is carried by blood in two forms; physical solution (dissolved oxygen in water of plasma and cells.), the volume of which is the product of PO_2 and solubility of oxygen (0.003 ml for each 1 mm Hg partial pressure). Accordingly, the arterial blood contains 0.3 ml of oxygen per dl; while the venous blood contains 0.12 ml of oxygen per dl. This dissolved oxygen determines the PO_2 , direction and rate of oxygen diffusion, and percentage saturation of hemoglobin with oxygen (SO_2). In addition, it provides oxygen to tissues with no red blood cells, for example the cornea and the lens of the eye.

Chemical form; oxygen combines with ferrous of hemoglobin to form (oxygenated hemoglobin). It is the storage form of oxygen, since about 98% of oxygen is bound to hemoglobin (34).

Oxygen-hemoglobin dissociation curve (ODC) is the standard graphical representation of the relationship between the (SO_2) and PO_2 when the P^H , P_aCO_2 , core body temperature, and 2,3 diphosphoglycerate (DPG) are normal (35).

SO_2 represents the overall percentage of binding sites on hemoglobin which are occupied by oxygen. In healthy individual breathing room air at sea level, S_aO_2 is between 96-98%. This is because normally less than 3% of the cardiac output is anatomically shunted. This shunting

occurs in the Thebesian veins, which drain into the left ventricle and bronchial veins which drain into the left atrium.

Oxygen carrying capacity is the maximum volume of oxygen which the hemoglobin can carry when fully saturated. Each gram of hemoglobin can carry 1.34 ml of oxygen when fully saturated. Normally, in 100 ml of arterial blood, 15 grams of hemoglobin will carry 20 ml of oxygen. Whereas, 100 ml of venous blood will carry 15 ml of oxygen (3).

Oxygen content is the actual volume of oxygen present in chemical form per 100 ml of blood. It is the product of hemoglobin concentration, PO_2 , and SO_2 .

Oxygen utilization (oxygen extraction) is the amount of oxygen taken up by an organ from arterial blood per minute of time. It is the product of arterio-venous difference concentration of oxygen multiplied by organ blood flow during the same period of time (Fick principle) (36). Following circulation through the tissues, the average oxygen saturation in the venous blood returning to the right side of the heart (mixed venous blood) is typically about 75% in healthy individuals at rest, a figure which implies a considerable delivery to the tissues.

At moderately high altitude the curve is shifted to the right side because of increased 2,3, diphosphoglycerate (DPG). In rightward shift, the affinity of hemoglobin to oxygen is reduced. The SO_2 for a given PO_2 is reduced. Thus, hemoglobin receives less oxygen at the level of the lung but releases relatively more oxygen at the tissue level (35).

However, small changes in 2,3, (DP re relatively unimportant and that the in vivo ODC is probably little different from that at sea level, at least at rest and up to altitude of 2.000 m (6.600 ft) (37).

Shifting of ODC at high altitude to either direction is part of acclimatization to reduced oxygen.

In leftward shift, the affinity of hemoglobin to oxygen is increased. The SO_2 for a given PO_2 is increased. Thus, hemoglobin picks up more oxygen at the pulmonary capillary level but delivers relatively less oxygen at the tissue level where the PO_2 is normally very low. At extreme altitude, the under corrected respiratory alkalosis will shift the curve to the left side. This shifting is beneficial in enhancing lung oxygenation to a greater extent than retarding oxygen release in the tissue (38). Factors affecting curve position are complex, and altering one or two of them does not guarantee that the individual will benefit (39).

It seems that, a coordinated interaction between the standard factors affecting the ODC is rather important than the position of the curve itself, for adequate tissue perfusion. Or the influence of the curve position on other factors which are potential to improve oxygen supply to the tissue (39).

POLYCYTHEMIA

Increased erythropoiesis is probably the best-known physiological response to chronic hypoxia and a hallmark of high-altitude acclimatization. Hypoxia induces the expression of glycoprotein hormone erythropoietin (EPO) which mediates the increase in red blood cell production. Once in the blood stream, EPO acts on the bone marrow and promotes the

survival, proliferation, and differentiation of erythroid progenitors by binding to its receptor (40).

Although EPO is expressed in several tissues, the cortical peritubular fibroblasts in the kidney are the primary site of EPO production, and responsible for its increased concentration in blood during hypoxia (41).

Within the first hours at altitude, serum EPO level rises; insensible water loss increases due to hyperventilation; and hypoxia-induced diuresis occurs. These three factors result in initial increase in red blood cell mass (42). EPO levels reach a peak on about the first to third day and then, even if the subject remains at altitude (sustained hypoxic stimulus), fall away in 5-10 days to levels only marginally above control (43). However, the red blood cell mass continues to rise for 3-6 months and remains stable during the length of altitude exposure (44). This phenomenon is known as EPO paradox (45).

CARDIOVASCULAR SYSTEM

At altitude above 700 m (2310 ft), acute hypoxia stimulates the peripheral chemoreceptors to activate the autonomic innervation of cardiovascular system with transient beneficial outcomes (46).

Sympathetic stimulation together with vagal withdrawal will increase the heart rate with consequent increase in cardiac output (47). Stroke volume do esn't contribute significantly in increase of cardiac output during acute hypoxia. This is because sympathetic-induced positive inotropic effect (decreased end systolic volume) is likely to be offset by a reduction in end-diastolic volume. Thus, the left ventricular ejection fraction is unaffected (48).

However, during severe acute hypoxia, myocardial contractile function is preserved at least to 4500 m (14.850 ft) (49).

This is primarily because of hypoxic-induced dilatation of epicardial coronary blood vessels (50).

This capacity of local control mechanism (vasodilatation) to override sympathetic vasoconstriction has been well described during normoxic exercise. All blood vessels are constricted with the exception of skeletal, coronary, and cerebral circulation. This phenomenon in physiology is known as functional sympatholysis (51).

High altitude hypoxia is a potent activator of the sympathetic nervous system, eliciting increases in sympathetic vasomotor activity (52). The increased sympathetic vasomotor outflow is mediated by baroreceptor reflex activity (53).

The systemic circulation dilates in the presence of hypoxia, in contrast to pulmonary circulation, which vasoconstricts. This response of the pulmonary circulation is known as hypoxic pulmonary vasoconstriction (HPV). It is a protective physiological reflex that aims to divert the blood flow away from hypoxic areas of the lungs to areas with better ventilation and oxygenation. It is a mechanism to match regional ventilation and perfusion with

consequent reduction of shunted blood and minimization of hypoxemia without increase in pulmonary arterial pressure (54). The exact underlying mechanism of HPV is not yet known. Reactive oxygen species may induce intracellular calcium increase and subsequent contraction of pulmonary artery smooth muscles via interaction with other mediators (55). Pulmonary vasoconstriction in acute hypoxia occurs in two phases, the first phase is mediated by reactive oxygen species (56).

In the second phase there is sustained reduction in vascular nitric oxide bioavailability combined with an increase in endothelial-derived vasoconstrictor (57). When the hypoxic stimulus is brief (a few hours), HPV is completely reversible upon restoration of normoxia or administration of supplemental oxygen (58).

At high altitude, acute alveolar hypoxia causes immediate generalized pulmonary arterial vasoconstriction, enhanced pulmonary vascular resistance, and increase in pulmonary arterial pressure. This HPV response is an immediate reaction to hypoxia which is measured as an increase in pulmonary arterial pressure (59). The physiological significance of HPV at low altitude is obvious in the presence of localized hypoxia in the lungs, for example pneumonia or lung collapse. Local alveolar hypoxia induces acute HPV, which is limited to the affected lung segments. However, with global lung hypoxia, HPV seems to be disadvantageous to those living at or going to altitude because of substantial increase in pulmonary vascular resistance and pulmonary arterial pressure, as a result of exaggerated HPV at the acute setting (60). This can lead to acute high-altitude pulmonary edema and chronic congestive heart failure (61).

It was reported, by Luks et al (62), that acute responsiveness of the pulmonary circulation to either hypoxia or hyperoxia not impaired during 12-13 days of progressive ascent from sea level to 5300 m (17.500 ft), suggesting that the pulmonary circulation maintains its overall responsiveness to changes in inspired PO_2 . Two weeks at 5050 m (16.700 ft) were required almost as a "threshold duration" to ablate pulmonary vasculature reactivity to supplemental oxygen fully (63).

After almost a month at the same above altitude, more severe hypoxia has no additional effect on HPV in lowlanders at altitude or high-altitude acclimatized residents (63).

Subedi et al. study adds another piece to the pulmonary puzzle that helps us to gain a better understanding of the development and the reversibility of high-altitude-induced pulmonary hypertension (64). The ventilatory acclimatization of lowlanders, going to high altitude, is characterized by progressive increase in ventilation, P_{aO_2} , and SO_2 along with normalization of arterial P^H . It is generally believed that the increased ventilation and decreased total body water (resulting in a reduced plasma volume) are the two vital physiological components of high-altitude acclimatization. This results in haemoconcentration facilitating the oxygen-carrying capacity of the blood with normalization of arterial oxygen content of the blood, after an approximately 7 days of residence at high altitude (65).

Most of high-altitude populations, in the world, reside in three central regions: the Himalayas of South-Central Asia (Tibetan/Sherpa), South America (Peruvian Andeans), and the highlands of eastern Africa (Ethiopian/ Amharas and Oromos) (66).

There are three successful patterns of human adaptation to high altitude hypobaric hypoxia: Andeans, Tibetan Sherpa, and Ethiopian pattern of adaptation (67).

The classic Andean pattern: Andeans reside at altitude of about 4000 m (13,200 ft) where the PO_2 is less than two-thirds of that at sea level. This sort of adaptation is characterized by arterial hypoxemia, moderately reduced SO_2 (68), and increased hemoglobin concentration (69).

Tibetans reside at the same altitude, their pattern of adaptation is characterized by arterial hypoxemia, significantly reduced SO_2 , and hemoglobin concentration similar to that of sea level population (70).

Tibetan highlanders show elevated resting ventilation with normal HVR, whereas Andeans highlanders have both low resting ventilation and low HVR. Tibetan highlanders have less pulmonary vasoconstrictor response to hypobaric hypoxia than Andeans and Ethiopians (71). Nitric oxide is a potent vasodilator that contributes to pulmonary arterial pressure regulation and is beneficial in management of pulmonary artery hypertension (72). Increased level of nitric oxide may be an adaptive response to high altitude hypoxia to promote blood flow and therefore increase tissue oxygen delivery (73).

Sustained sympathetic activity in lowlanders during high altitude acclimatization demonstrated 180% increase in muscle sympathetic nerve activity (MSNA) within 10 days of exposure, and is maintained for duration of altitude exposure, at least up to 50 days (74).

Tibetan Sherpa have adapted to favor an overall lower sympathetic vasomotor outflow compared with acclimatizing lowlanders while having similar resting arterial blood pressure and similar or lower reactivity to heightened sympathetic stress (75).

These lower levels may represent beneficial hypoxic adaptation in Sherpa. The effect of high-altitude hypoxia on arterial baroreflex control on MSNA is unknown. Acute hyperoxia at high altitude had minimal effect on baroreflex control of MSNA in lowlanders and Sherpa, raising the possibility that mechanisms other than peripheral chemoreflex activation contribute to vascular sympathetic baroreflex control (75).

In contrast high-altitude populations in the Andes exhibit a high reported incidence of excessive erythrocytosis (defined as hemoglobin of more than 21 g/dl in males and more than 19 g/dl in females), which has been linked with increased risk of cardiovascular disease (68). Interestingly, excessive erythrocytosis is extremely rare in Tibetan high-altitude natives (70).

THE ETHIOPIAN PATTERN

Amhara highlanders live at the top of the Simien Mountain of northern Ethiopia at altitude of 4550 m (15,000 ft) which is the highest peak in Ethiopia and the fourth in Africa. Their pattern of adaptation is characterized by hemoglobin concentration, P_{aO_2} , and SO_2 values similar to that of sea level (67). Normal P_{aO_2} despite inevitable hypobaric reduction of PIO_2 is a puzzler and big challenge to respiratory physiology.

Traditionally, increased hemoglobin concentration has been considered as a cornerstone of chronic adaptation to high-altitude hypoxia (76). Erythrocytosis maintains oxygen content of arterial blood (77). The falsity of this belief is proved by the unique adaptation of Amhara highlanders living in the Simien mountains of Northern Ethiopia.

The native Amhara highlanders, like Tibetans, have increased nitric oxide and cyclic guanosine monophosphate (78). This suggests the possibility of adaptation via vasodilatation, which would improve oxygen supply to metabolic tissues (67).

How this vasodilatation can be an adaptive response?

Hypothetically, this could be due to increased pulmonary capillary transit time which is an important variable of gas exchange (79).

The resistance of movement of oxygen across alveolar-capillary membrane doesn't only reside in the barrier between the pulmonary capillary blood and alveolar gas. Some of the diffusion resistance is located within the capillary and the interior of the red blood cell (80). In addition, there is also resistance to gas transfer which is caused by the time taken for hemoglobin to react with oxygen (finite reaction). Finite reaction is the rate in ml per minute of oxygen which combines with 1 ml of blood per 1 mm Hg partial pressure difference of oxygen. When this multiplied by the volume of capillary blood will give the effective diffusing capacity of the rate of reaction of oxygen with hemoglobin (81).

Vasodilatation will increase pulmonary blood flow with consequent increase in the overall diffusing capacity of the lung. In Amharic population, because of lack of hypoxic stimulus, pulmonary vascular resistance is not increased (82). Oxygen uptake in the lung is limited by short capillary transit time (83).

Capillary transit times are very heterogenous under resting condition but homogenize as blood flow and oxygen demands increase (84). In muscle tissue homogenization is accompanied by an increase in hematocrit, further increasing the number of oxygen-carrying erythrocytes across capillaries at any given time (85). Note that higher hematocrit increases the oxygen concentration in capillary blood and represents an instance of prolonged capillary transit times for cells (erythrocytes only) (86). It could be hypothesized that oxygen-carrying capacity of hemoglobin among Amharas is higher than that of another highlanders' population.

An impressive effect of the infection with SARS-Co-19 is the impairment of oxygen uptake due to lung injury (87).

Boning et al (88) demonstrated that left shifting of ODC in patients with COVID-19 was related to good prognosis. The mechanism of which is not known. A possible explanation is that COVID-19 counteracts the unfavorable large right shift of the oxygen dissociation curve in these patients (89).

A relevant influence of nitric oxide on hemoglobin oxygen affinity is disputed because of its very low concentration compared to hemoglobin at sea level (90). However, nitric oxide production is increased among indigenous Amhara highlanders (78). This results in left shift

of ODC which makes Amharic high-altitude natives better suited for survival at high altitude. The mechanism by which left shift of ODC provides this privilege is not known.

A big challenge to respiratory physiology is normal P_{aO_2} in Amharas despite low ambient P_{O_2} . Oromos population living in the Bale mountains of southern Ethiopia at 3530 m (11,700 ft) have elevated hemoglobin, arterial hypoxemia, and reduced SO_2 (91,92).

The brain receives 15% of resting cardiac output. It is the most oxygen-dependent organ in the body which consumes 20% of resting oxygen consumption (93).

The mechanisms which control cerebral blood flow as well as influence of high-altitude exposure on these mechanisms are not clear. Blood flow in arteries is determined by cerebral perfusion pressure and cerebrovascular resistance (94). Acidosis improves cerebral blood flow by contrast, alkalosis decreases cerebral blood flow (95). Hypoxia per se is a peripheral vasodilator; however hypoxia-induced hyperventilation (hypocapnia) results in vasoconstriction. That is to say, people exposed to chronic hypoxia, as at high-altitude, are at a risk of constriction of cerebral vessels and reduction of cerebral blood flow (96). The balance between the degree of hypoxia and hypocapnia is a critical determinant of cerebral blood flow at high altitude (97).

The cerebral circulation of high-altitude Amharic natives is sensitive to nitric oxide and carbon dioxide but not to hypoxia (67). This results in increased cerebral blood flow with consequent delivery of enough oxygen to the brain. Therefore, the Amharas are more potential to survive at high-altitude. Most of the manifestations of chronic mountain sickness are due to neuronal hypoxia (98).

That is why this maladaptation to chronic high-altitude hypoxia disorder is extremely rare in indigenous native Amharic high-altitude residents (67).

CONCLUSION

Of the three successful patterns of adaptation to high altitude chronic hypoxia; the Amharas have the legend one. Normal P_{aO_2} despite inevitable hypobaric reduction of P_{IO_2} is a puzzler and big challenge to respiratory physiology.

Amharas have elevated nitric oxide which is potential to stand as vasodilator adaptive response which enhances blood flow to tissues.

Left shift of ODC under influence of nitric oxide seems to be an integral component of Amharic pattern of adaptation. The mechanism of which is not known.

It could be hypothesized that native Amharas highlanders have increased, pulmonary capillary transit times; finite reaction of hemoglobin with oxygen; and oxygen-carrying capacity of hemoglobin than other high-altitude populations.

Further research is warranted to explore the physiologic mechanism by which Amhara highlanders maintain normal P_{aO_2} despite hypobaric hypoxia. This is a potential breakthrough in management of critically ill hypoxic patients at intensive care settings.

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