Cardio Respiratory Adjustments to High Altitude

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Thousands of Indian lowlanders live and work at altitudes up to 6,400m in the western Himalayas for durations up to two years, and are exposed to hypobaric hypoxia and intense cold. Here, certain unique physiological changes occur in these individuals and they could also be affected with the well-known maladies of high altitude, i.e. acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), high altitude cerebral edema (HACE) and cold injuries. This review describes cardio respiratory changes occurring on acute induction of subjects to high altitude and during their acclimatizing period. In addition, it also outlines the pathophysiology, treatment and prevention of the common high altitude (HA) maladies.

Introduction

India is unique in having thousands of lowlanders staying at altitudes up to 6,400m where the challenge is not only to be free from disease but also to ensure the best performance in physical and psychological terms. Here, they encounter hypobaria, hypoxia and extreme cold conditions, which could lead to acute mountain sickness (AMS) and in extreme conditions to high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). Altitudes higher than 3,000m are considered as high altitude (HA) and extreme altitude is higher than 5,500m [1-3]. The percentage of oxygen in air is not different from what it is at sea level (i.e. 20.09%) but owing to the lower ambient atmospheric pressure, there is an absolute reduction in the partial pressure of oxygen in the air being breathed in. A sufficient oxygen supply to the brain and the vital organs is ensured by the initiation of numerous physiological responses to hypoxia which may last for minutes to days [4]. There is an orchestrated effort by the body to combat the stress of ambient hypobaric hypoxia, which is a unique phenomenon when compared to pathological regional hypoxia, which occurs in many pulmonary diseases. The failure of the protective reflexes to effectively play their role, also called ‘Hyperexis’ is well elucidated in the adjustments the body makes at HA. On ascent to high altitude the immediate changes that occur in the cardio respiratory system and the problems of malacclimatisation also target these mechanisms [5, 6]. A review of the current concepts in cardio respiratory adjustments to HA is presented here.

Hyperexis and High Altitude

Hyperexis is a state whereby a homeostatic response that ordinarily protects the body, begins to have damaging effects. A typical example of this at HA is hypoxic vasoconstriction of pulmonary arterioles, a reflex that is normally beneficial to patients of obstructive lung disease as the local pulmonary vasoconstriction diverts the blood flow to better-aerated alveoli. However, it becomes useless or even detrimental when the whole lung experiences hypoxia as in hypobaria [7, 8].

An increase in hemoglobin concentration is usually considered an appropriate response to low PaO₂ (Partial pressure of oxygen in arteries) as it maintains SaO₂ (peripheral saturation of oxygen) to such values that cardiac output remains within the normal range. But this adaptive response as seen in HA, defeats its very purpose by increasing blood viscosity. This increased viscosity alters the hemorrhheological properties of the blood and has a contributory role to play in the increased thrombotic tendencies at HA causing deep vein thrombosis, stroke in young, and splenic infarcts [9, 10]. Studies have also been done to show the contributory role of increased viscosity in pulmonary hypertension by creating disturbances at the microcirculatory level and this may become an additional medical problem [11].

Respiratory System

As soon as one reaches high altitude, the peripheral chemoreceptors sense hypoxia and cause an increase in ventilation. This may be seen within the first few minutes of arrival at HA and being manifest as an increased tidal volume and respiratory rate, washes out the alveolar CO₂ so the hypocapnia that is produced, leads to alkalosis. An increase in the duration of stay leads to ventilatory acclimatization and the hypocapnia and alkalosis disappear over the next few weeks. There are individuals who show a less than expected increase in ventilation during the first day of induction to high altitude. This has been explained as the phenomenon of hypoxic ventilatory decline [12-14]. In such individuals this
hypocapnic alkalosis coupled with hypoxia plays an important role in the regulation of respiration. In the normoxic environment, the central regulation of respiration is CO₂-dependant but in a hypoxic one, the oxygen levels along with hypocapnic alkalosis determine the respiratory drive. This is considered as the primary cause of sleep disturbances and periodic-breathing at high altitude [15-17]. Since acetazolamide is able to reverse this hypocapnic alkalosis, it is considered as the sleeping tablet of choice at high altitude [18].

**Hypoxic Ventilatory Response (HVR):** This is an index for measuring the ventilatory response of an individual to hypoxia either in a simulated, or in a naturally occurring environment. The more vigorous the ventilatory response to hypoxia, the higher will be the levels of alveolar PO₂ (partial pressure of oxygen) and greater will be the expected levels of arterial PO₂ and arterial oxygen saturation. The magnitude of individual variability in HVR is quite high and thus we have high and low responders [19, 20]. Inter-individual variability in HVR appears to have a genetic basis [21]. Presumably a higher HVR, by elevating PaO₂, should be an asset at high altitude. Endurance athletes commonly possess a low HVR, the benefits of which during performance might well be seen as a lower metabolic cost of ventilation and less accompanying dyspnoea [19]. Observations on the climbing performance of several Himalayan expeditions suggest that those possessing high HVR tend to perform better than those with low HVR. Individuals with lower HVRs may be more susceptible to acute high-altitude illnesses, including acute mountain sickness (AMS) [22–25] and high altitude pulmonary edema [26, 27]. For lowlanders acclimatizing to high altitude, a brisk HVR seems to confer an advantage, combining both lower susceptibility to acute illness of high altitude and an enhanced capacity to perform physical work at extremely high altitudes. Studies on permanent residents of high altitude have revealed that each ethnic group of native highlanders are unique in their adaptive mechanisms to enable them healthy living at HA. Studies conducted by Severinghaus et al. [28] found that Andeans had a blunted HVR as did the Sherpas living in the Himalayas as found by Lahiri et al. [30]. More recently Zhuang et al. and Beal et al. also found blunted HVR in high altitude natives of Tibet and Ayamara [29, 31].

**Ventilatory Acclimatization:** This occurs primarily because of carotid body hypoxia. It has been observed by Lahiri et al. [32] as well by others [33] that the afferent discharge of the carotid sinus nerve increases over a period of time during hypoxia. Interestingly, it has also been seen that the same is not true for hypercapnia i.e. an increase in the partial pressure carbon dioxide in the inspired air [27, 28]. The neurotransmitters involved in this are dopamine, nor-epinephrine, nitric oxide, substance P, ANP and other kinins [34]. Regulation of pH of the CSF also appears to play a significant role in the process of acclimatization as the latter is slowly regulated back to normoxic levels and appears to restore the central ventilatory drive which had been inhibited by alkalosis [35, 36].

**Oxygen Transport at High Altitude:** PO₂ falls at each stage as oxygen is transported from the air breathed into the lungs into the alveoli, from where by systemic circulation it goes into the arterial and mixed venous blood. This forms a staircase or a cascade of PO₂ levels. The process of acclimatization can be thought of as reducing each step in this cascade as far as possible [37]. From ambient air to the inspired air there is a drop of 47 mm Hg because of humidification and this drop does not change at high altitude. The PO₂ of dry air at sea level is about 160 mm Hg (20.9%) of 760 mm Hg, or the barometric pressure at that location. At an altitude of 5,800m the barometric pressure is about half of that at sea level, so the ambient PO₂ is also half of that of sea level value i.e. 80mm Hg. At sea level there is a drop of about 50 mm Hg from the inspired to the alveolar air in the oxygen transport system. After acclimatization at 5,800m resting alveolar ventilation is approximately doubled and the reduction in alveolar PO₂ at this step in the system is halved. Oxygen passes across the alveolar-capillary membrane by diffusion resulting in a small drop in pressure in the normal lung and this accounts for less than 1mm Hg. The total alveolar-arterial (A-a) PO₂ gradient at sea level is about 6-10mm Hg. At high altitude, at rest there is little change in the (A-a) PO₂ gradient from its value at sea level. The increase in pulmonary artery pressure due to hypoxia reduces the gravitational effect on the distribution of blood flow in the lung. Hence in this part of the cascade there are many unexplained factors since the ventilation-perfusion ratio, the degree and distribution of hypoxic vasoconstriction is different in different individuals and also varies in the same individual during different inductions to high altitude. The last level of drop in PO₂ from arterial to mixed venous is due to the uptake of oxygen in the tissues. Increase in hemoglobin concentration is probably the best-known feature of acclimatization, to influence this step [38].

**Work of Breathing at High Altitude:** There are two important aspects affecting the mechanics of breathing. The first is, that air that is less dense makes breathing rapidly easier [4]. It could explain how mountaineers while climbing towards the summit of Mt Everest (8,840m), tend to breathe at a rate of 60-62 times per minute (with total ventilation = 207.2 L/min) [4, 39]. The second issue is that of hypoxia itself affecting the musculoskeletal dynamics of breathing. Beyond 6,000m altitude the limiting factor for physical performance is only hypoxia and at this juncture as much as 10% of oxygen consumption is only for the work of breathing [6, 39]. The work of breathing increases with increasing...
altitude but a proportionate increase in alveolar and arterial oxygen is not seen.

**Cardiovascular System**

The cardiovascular system carries oxygen to all the different parts of the body. It may be noted that the entire cardiovascular system including the cardiac variables such heart rate, stroke volume, cardiac output and vascular factors like pulmonary vasoconstriction, systemic vasoconstriction initially as a response to sympathetic discharge and vasodilatation Thereafter, they respond as one to acute hypoxia, in order to minimize its effects. This starts with an immediate tachycardia, hemoconcentration, changes in stroke volume, cardiac output and myocardial contractility, changes in systemic and pulmonary blood pressures.

**Right Heart:** The functions of the right side of the heart and related pressures play a significant role in the physiological adjustments on induction to high altitude. Related to the function of the right heart, is a significant hypoxic pulmonary vasoconstriction which increases the after-load of the right ventricle and finding individuals with right ventricular strain as seen in the ECG, right ventricular dilatation, pulmonary hypertension and pulmonary thromboembolism. Echocardiography is commonly used for studying right heart function and pulmonary arterial pressures (PAP) while at high altitude [40-42]. On induction to high altitude the vasoconstriction response is indicated in the PAP recordings, which clearly show pulmonary hypertension. This sustained pulmonary hypertension is also known to cause right heart failure [43]. The occurrence of hypoxic vasoconstriction is seemingly variable in apparently healthy individuals [44]. This difference is attributable to endogenous pulmonary vascular endothelial nitric oxide, vascular smooth muscles, K+ and Ca2+ ion channel proteins and other mediators [45-47]. The mechanism of this hypoxic pulmonary vasoconstriction appears to be local and not central [48-51]. Studies have shown that the alveolar oxygen and not pulmonary arterial oxygen which causes vasoconstriction [52]. The site of this phenomenon is the small-sized arteries [52, 53]. Another aspect is that of vascular remodelling that occurs in response to this raised PAP [52-57]. This view is supported by the finding that in HAPE the raised PAP causing mechanical damage to the capillaries and making them leak to cause edema, seldom occurs after seven to nine days [58-60]. This is explained by the observation made by several others that arteries get hypertrophied or muscularised and this appears to be protective against development of HAPE [60]. Contrary to this, the well-adapted high altitude animal like the yak has very thin arteries. Post-mortem studies on native Ladakhis have also revealed that they lack the medial thickening in their arteries [61]. The genetic switching on for synthesis of special proteins for muscularisation is seen as early as 4 hours after entry into high altitude [61]. It has also been seen that medial thickening and hypertrophy occurs in individuals who have spent significant time in high altitude and it is also normally seen in native high landers [54, 61]. Muscularisation occurs a few days after vasoconstriction [62-64]. Based on the assumption that raised PAP might be limiting physical performance at high altitude, some studies have tried out interventions to reduce PAP and promote performance. Few studies describe the use of Sildenafil Citrate to improve performance [65, 66]. A raised PAP causing pulmonary edema has been known since long (58-60, 67-71) and in this, interventions such as Inhaled Nitric oxide, oral Sildenafil have shown promising results in the treatment of HAPE [65, 66, 72].

**Cardiac Output, Heart Rate, Stroke Volume:** There is a rise in cardiac output on acute induction more because of increased heart rate than due to a significant increase in stroke volume. After a few weeks, the cardiac output shows a downward trend, heart rate reduces though never to that of sea level values and the stroke volume shows a reduction directly proportional to the height at which the individual is at [73-75]. This increase in heart rate is mainly due to sympathetic activation but also due to vagal withdrawal [76-78].

**Peripheral Vessels:** Inspite of sympathetic outflow with hypoxia, vasodilatation is seen in all vascular beds with the exception of that in the lungs [79, 80]. Blood pressure depends on which of the above two dominates. The level of systemic blood pressure also depends on altitude that the individual is inducted to and the arterial oxygen levels. Unlike as seen in the Caucasians [81], the acclimatized lowlanders of Indian origin have systemic hypertension which according to the studies is believed to be caused or aggravated by High Altitude and may be because of sustained sympathetic overdrive besides genetic peculiarities in the ACE gene [82].

**Syndromes of Maladjustments and Malacclimatisation to High Altitude:** Acclimatization, on entry to high altitude, is important for a healthy sojourn (Fig 1). Considering the innumerable systemic adjustments for a healthy and uneventful sojourn at high altitude, it is not surprising that lowlanders at high altitude suffer from a peculiar spectrum of disorders that are unusual to sea level. The significant ones are acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), high altitude cerebral edema (HACE) and sub acute mountain sickness (SAMS).

**AMS:** This is classically described in many studies and now there is a universally accepted scoring system i.e. Lake Louise Scoring which makes its diagnosis very objective [83, 84]. AMS is characterized by one or more of the following features: headache, light-headedness, breathlessness, fatigue, insomnia, anorexia, and nausea. Typically, these symptoms are seen 2 or 3 hours after
Ascent, but the condition is generally self-limiting and most of the symptoms disappear after 2 or 3 days. However, disturbances of sleep may persist [85]. AMS occurs in more than 50% of individuals coming to high altitude [86]. It is self-limiting in the first 24-48 hrs and does not warrant any intervention. However medication to alleviate the distressing symptoms becomes necessary if they are extreme in nature, intolerable or persistent. The pathophysiology, though not very well understood, indicates a definite role of an increase in cerebral blood volume because of hypoxic cerebral vasodilation [87, 88]. In fact, AMS and HACE are now accepted as the two extreme ends of the same pathophysiology, and preventing AMS therefore, is of all importance. Staged ascent and acetazolamide are the two recommendations of preventing and reducing AMS [89-91].

**High Altitude Pulmonary Edema (HAPE):** In healthy young males who are recently inducted to high altitude, this is typically seen as an exaggerated hypoxic vasoconstrictor response (Fig 2) with PAP greater than 45mm Hg, a low SpO2, tachypnoea, tachycardia, cough with pink frothy sputum and typical radiological signs on chest radiograph Fig 3 which responds dramatically to rest, oxygen and descent [58-60, 92]. Not all is known about the pathophysiology of HAPE but there is definite evidence that there is pulmonary hypertension and changes in the permeability of the pulmonary vascular endothelium which makes the edema a protein rich transudate [93-97]. The deficiency of Nitric oxide was seen in individuals who have HAPE highlights a definite role for nitric oxide in the pathophysiology [98, 99]. The prevention of this disorder is one of the active areas of research but as yet the success is limited. Nifedipine, Salmeterol, Dexamethasone and Tadalafil are a few drugs, which have proven to have some useful affects [100-102].

**High Altitude Cerebral Edema (HACE):** High-altitude cerebral edema (HACE) is considered to be an extreme form of AMS. This is the most fatal of all the high altitude problems with almost 100% mortality if not treated in time. It has been identified as a vasogenic edema and as many as 5% of the cases may develop life-threatening high-altitude cerebral edema (HACE) [103, 104]. Increased intracranial pressure and cerebral edema are documented in moderate to severe AMS, suggesting exacerbation of AMS to HACE [105-108]. These findings led to some understanding of the pathophysiology of AMS and ultimately to considering a role for vasogenic cerebral edema, elevated cerebral blood volume (CBV), brain swelling, fluid retention/redistribution and intracranial hypertension in AMS and HACE. Hypoxemia is translated through a series of cellular, molecular and physiological signals ultimately to cause brain swelling due to cerebral edema and elevated CBV. The sum of these peripheral responses to hypoxia influences the blood brain barrier (BBB) permeability leading to cerebral edema. These changes increase the intracranial pressure leading to HACE [102-
110]. Classically, the patient becomes confused and ataxic and may experience mood changes. Hallucination has also been described, and serious cases involve coma followed by death. On examination, the patients may have papilledema and occasionally, focal neurological signs affecting the cranial nerves, or in some cases even hemiparesis. The treatment modalities include Dexamethasone, Diamox, Mannitol, Oxygen, placing the patient in a compression chamber if descent is not possible. However descent to lower altitudes is the best treatment [105].

**Sub Acute Mountain Sickness**

This term is used in two different conditions. The first one is a condition that occurs in infants at high altitude who present with respiratory distress, marked cyanosis, and congestive heart failure [111]. The other, affects young adults especially the soldiers of Indian army who are posted to altitudes of approximately 6,000m for many months and develop dyspnea, cough, angina at effort, and dependent edema [112]. These conditions may be related to so-called brisket disease in cattle [113] which is a form of right-heart failure with peripheral edema seen at high altitude.

**Conclusion**

High-altitude is characterized by low PO₃ in the inspired gas, which results from the reduced barometric pressure. The deleterious effects of high altitude are greatly reduced by the process of acclimatization, the most
important feature of which is hyperventilation caused by hypoxic stimulation of peripheral chemoreceptors. The response of the cardio respiratory system is a well-orchestrated event that occurs with the main aim of improving the availability of oxygen to the tissues. It usually consists of hyperventilation leading to the undesirable hypocapnic alkalosis. This is followed by hemococoncentration, initially as a result of diuresis and later by increased hemopoiesis, tachycardia, minimal decrease in cardiac output, significant rise in pulmonary pressure resulting in right heart strain and rise in systemic blood pressures. Extraordinary physiologic adaptations occur at extreme altitudes, e.g. at the summit of Mount Everest, where the arterial PO$_2$ is approximately 30 mm Hg, PCO$_2$ is less than 10 mm Hg, and pH over 7.7. However if these are not adequate adjustments, they lead to high-altitude diseases like acute mountain sickness, high-altitude pulmonary edema, high-altitude cerebral edema and sub-acute mountain sickness. Acute mountain sickness is usually self-limiting and often resolves after 2 or 3 days. High-altitude pulmonary edema is much more serious, and recent work indicates that the mechanism involves damage to pulmonary capillaries caused by uneven hypoxic pulmonary vasoconstriction. High-altitude cerebral edema can be fatal and the mechanism is poorly understood. Sub-acute mountain sickness occurs as a syndrome of right heart failure seen in infants and young Indian adults. All of these conditions can be overcome successfully by immediate descent.

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