

“The Himalaya is a great deva-atma, a great spiritual presence, stretching from the west to the eastern sea like a measuring rod to gauge the world’s greatness.”

Kalidasa.

INTRODUCTION

Mankind has been fascinated by mountainous regions of the world from the time immemorial. More than 400 million people permanently reside at elevations above 1500 meters above the sea level¹ while an estimated 40 million people travel and stay temporarily for leisure, sports, adventure, mining, scientific studies and for many other reasons including religion.² Many of Indian yogis have made Himalayas their permanent abode and live there with nature without any special protection. India has a large border with her neighbours stretching across the Himalayan and Karakoram ranges and Indian troops stay there for many months in extreme hostile conditions as prevalent in higher regions of Ladakh such as Siachen glacier which is considered as the highest battle field in the world. Indian subcontinent has some of the highest mountains in the world namely: Mount Everest (8,848 meters, 29029 feet), K2(Godwin Austen-8,611 meters,28251 feet), Kangchenjunga (8,586 meters, 28169 feet) and Nanga Parbat (8126 meters, 26660 feet). These mountains have been climbed several times and continues to be formidable and risky to many who continue to venture to these heights.

HIGH ALTITUDE

High altitude is defined as regions above 2400 meters above the sea level (8000 feet). It is further divided in to very high altitude-3500 meters to 5500 meters (11,500–18,000 feet) and extreme high altitude- more than 5500 meters (>18,000 feet). More than 140 million people, almost 2% of world’s population dwell in high altitude regions of the world.³ High altitude regions are found across continents in Himalayan mountains and Tibetan plateau of Asia, high lands of Ethiopia and Andean mountains of South America (Figure 1).⁴

Exposure to high altitude is a physiological stress due to prevailing extreme environmental conditions there and therefore, human survival becomes possible by physiological adaptations to such conditions. Permanent human habitation is difficult beyond 5500 metres. Respiratory system plays a significant role in determining survival and undergoes series of adaptive changes to compensate for hypobaric hypoxia and optimise tissue delivery and utilisation of oxygen. In the event of failure of adaptation, there is an imminent risk of developing altitude related sickness that can affect the one globally but lungs are commonly affected.

Conditions special to high altitude: Unlike at sea level, high altitude has a unique environment characterised by hypoxia, hypobaria and low temperatures. At sea level the barometric pressure is 760 mm of Hg with a partial pressure of inspired oxygen of 159 mm of Hg (FIO₂ of 20%) while the barometric pressure is 253 mm of Hg with

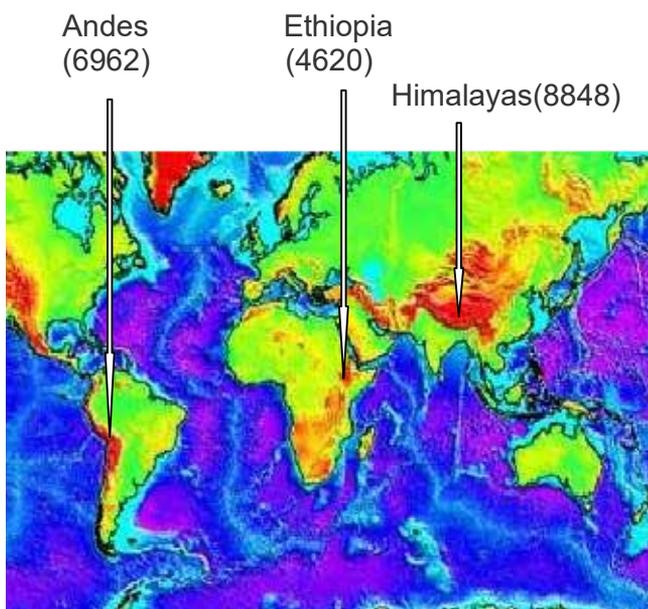


Fig. 1: Arrows depicting High Altitude regions of the world

Table 1: Altitude, Barometric Pressure and Inspired Partial Pressure of Oxygen

Altitude (meters)	Altitude (feet)	Barometric Pressure (mm Hg)	Inspired PO ₂ (mm Hg)
0	0	760	159
1000	3280	674	141
2000	6560	596	125
3000	9840	526	110
4000	13,120	463	97
5000	16,400	405	85
6000	19,680	354	79
8000	26,240	268	56
88848	29,028	253	43

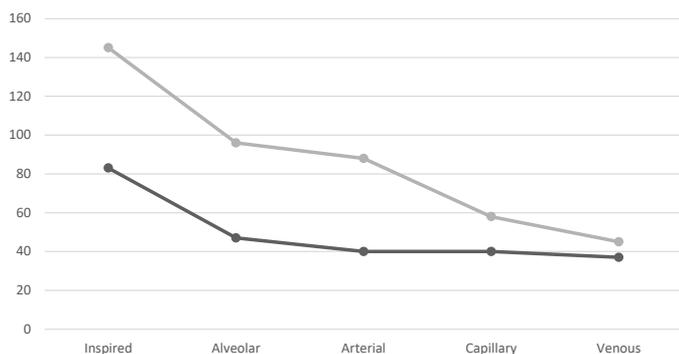


Fig. 2: Oxygen cascade at both sea level and 4450 meters

partial pressure of inspired oxygen of 43 mm of Hg (FIO_2 8%) on the summit of Mount Everest (Table 1).

This decline in partial pressure of oxygen in the air, as one gains height results in lower partial pressure of oxygen (PO_2) at every step in the oxygen transport chain as oxygen moves from atmosphere to tissue as to result in less availability of oxygen for oxidative phosphorylation in the mitochondria of the cell. Oxygen cascade both at sea level and high altitude are depicted in the Figure 2.

RESPIRATORY SYSTEM IN HIGH ALTITUDE

Respiration both external and internal leads to delivery of oxygen to tissue from atmosphere. In high altitude due to prevailing hypobaric hypoxic conditions, subjects who are exposed such an environment have to undergo series of adaptations in various steps of oxygen transportation to overcome tissue hypoxia as a result of less availability of oxygen for gas exchange, oxygenation of blood and cellular oxidative phosphorylation. These adaptations are complementary and are acute (immediate to 5 days), subacute (over weeks), chronic (months to years) or lifelong depending on the duration of high altitude exposure.

Ventilation

On rapid ascent to a height of more than 1500 meters, there is a marked increase in ventilation within few hours of exposure due to hypoxia induced respiratory stimulation via carotid body to minimise fall in alveolar PO_2 (PAO_2) as a result of fall in barometric pressure.⁵ This hypoxic ventilator response (HVR) results in decrease in alveolar PCO_2 in order to increase PAO_2 for compensating lower partial pressure of oxygen in the blood (PaO_2). At Mount Everest with barometric pressure of 253 mm of Hg and partial pressure of oxygen in the atmosphere of just 43 mm of Hg, PAO_2 is maintained around 34 mm of Hg due to hyperventilation when alveolar PCO_2 falls to 13 mm of Hg.⁶ HVR is related to degree of hypoxia and greater response is expected when arterial PO_2 (PaO_2) is below 60 mm of Hg.^{7,8}

Hyperventilation at a given altitude persists over a period of weeks and tends to normalise after few weeks of de-induction to a lower altitude.⁹ Over a period of days to weeks of stay in high altitude, oxygen saturation of blood improves due to sustained hyper ventilation after abrupt initial drop on acute high altitude exposure (Figure 3).

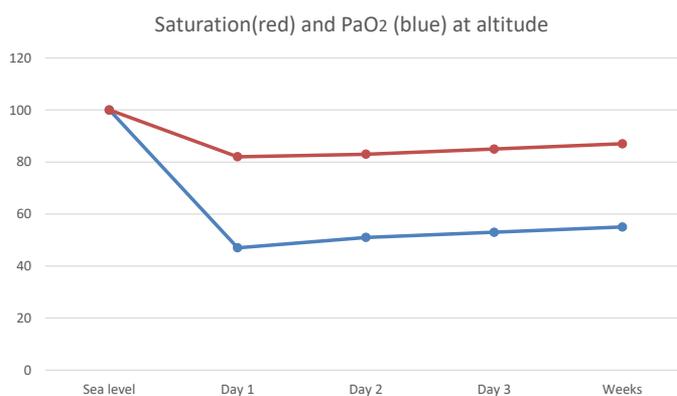


Fig. 3: Arterial saturation (blue) and arterial oxygen tension (red) before at sea level and during sudden high altitude exposure

This sustained hyperventilation despite hypocapnea is considered to be due to relative metabolic and CSF acidosis following bicarbonate loss in the urine for compensating respiratory alkalosis. However, this classic explanation attributing metabolic acidosis for sustained altitude related hyperventilation is being questioned since PH of both blood and CSF remains alkaline so also that of interstitial fluid and intracellular fluid of the brain despite alkaline urine. Further PH of both blood and CSF normalises soon after de-induction yet hyperventilation persists for few weeks. It is likely that augmented sensitivity of carotid chemoreceptors to hypoxia and mediators such as erythropoietin and hypoxia-inducible transcription factor 1 alpha ($HIF-1\alpha$) are some of the contributing factors for this ventilatory acclimatization.^{10,11} It may be noted that at higher ventilator rates as one ascends higher, oxygen demand for breathing increases and net gain in oxygenation by compensatory ventilatory response is traded off by the increased cost of breathing.

Breathing pattern changes in high altitude due to response of both central and peripheral chemoreceptors to dynamic changes and oscillatory pattern of oxygen and carbon dioxide levels in the blood.¹² Hyperventilation leads to carbon dioxide wash out with spells of apnea due to fall in partial pressure of carbon dioxide in the blood (PCO_2) below the threshold that is required to stimulate central chemoreceptors. Periodic breathing with recurrent episodes of apnea and hyperpnea is a feature among healthy people at high altitude that can occur at a modest height of 2500 meters during both wakefulness and different stages of sleep.^{13,14} At extreme high altitude above 5500 meters, periodic breathing disappears due to high frequency of breathing.^{15,16} Central sleep apnea is a feature in both highlanders and sojourners resulting in steep fall in oxygen saturation during apneas and arousals during hyperpneas. It is a contributing factor for severe hypoxemia that leads to altitude related illnesses.¹⁷

Lung functions in high altitude subjects show reduced gas exchange, fall in vital capacity, increase in residual volume, peak expiratory flow and total lung capacity. Lowlanders exposed to high altitude have lower vital capacity due to changes in pulmonary mechanics due to hypoxia and

258 hypcapnia. There is air way narrowing, increase in interstitial fluid, hypoxic pulmonary vasoconstriction, VQ mismatch and decreased muscle strength. On the other hand, highlanders have lower minute ventilation compared to lowlanders at high altitude under similar atmospheric conditions due to carotid body hypertrophy and blunted chemoreceptor response to hypoxia. They have advantage of higher vital capacity, reduced cost of breathing and increased exercise capacity.^{18,19,20}

Perfusion

Lung perfusion is inhomogeneous in both health and disease. Alveolar hypoxia causes hypoxic pulmonary vasoconstriction to facilitate redistribution of blood in various zones of lung to match ventilation and optimise diffusion of oxygen from alveoli to blood.²¹

Diffusion

Decreases with high altitude due to decrease in pressure gradient across alveolar capillary membrane that cannot be compensated even with a resting transit time of 0.75 seconds. Diffusion further decreases with shortened transit time following exercise.²² As a result, PaO₂ is lowered and is in the range that falls in to the steep portion of the oxygen dissociation curve. This results in marked decrease in oxygen content of the pulmonary capillary blood even with a small decrease in PaO₂. Long term residents of high altitude have less alveolar arterial oxygen difference, better diffusing capacity and higher mean PaO₂ compared to lowlanders exposed to high altitude.

Pulmonary circulation

The pulmonary circulation is a high-flow, low-pressure system.²³ At altitude the entire lung is hypoxic and hypocapnic. Vasomotor tone of pulmonary vasculature is largely due to the local effects of oxygen and carbon dioxide. Hypoxia causes acute pulmonary vasoconstriction that can be reversed by oxygen inhalation. Hypoxic pulmonary vasoconstriction has substantial inter-individual variability and results in acute elevation of pulmonary pressures that becomes substantial when PAO₂ falls below 70 mm of Hg.²⁴ It may be noted that acute effects of high altitude are due to dramatic changes in pulmonary hemodynamics without appreciable changes in pulmonary mechanics.

Chronic hypoxia in high altitude residents brings out structural changes-intimal fibrosis, smooth muscle hypertrophy and collagen proliferation with remodelling of pulmonary vasculature that cannot be reversed by correcting hypoxia. As a result, there is sustained increase in resting pulmonary arterial pressure and pulmonary vascular resistance. It takes several weeks to months after return to sea level for normalisation of right ventricular hypertrophy and pulmonary vascular pressures in such cases.²¹ Andean highlanders have high pulmonary artery pressures and descent to sea level or normal oxygen tension does not restore pulmonary artery pressure or right ventricular hypertrophy to normal levels. In contrast, Tibetan highlanders have minimal elevation of

pulmonary artery pressure and do not exhibit the vascular changes of the Andean highlanders.²⁵

Cardiac Output

Ascent to altitude augments cardiac output by increasing the heart rate without any concomitant increase in the stroke volume. In-fact, there is decrease in the stroke volume due to decreased plasma volume as a result of alkaline diuresis, natriuresis and respiratory fluid loss due to hyperventilation.²⁶ Myocardial depression that can occur with severe hypoxia is not the usual cause for low stroke volume. Upon acute exposure to altitude there is elevation of systemic blood pressure and increase in vascular resistance due to augmented sympathetic activity. Prolonged stay in high altitude is likely to reduce peripheral vascular resistance due to vasodilatory effect of hypoxia on peripheral circulation.

Oxygen transport On exposure to high altitude PaO₂ levels are found in the steep portion of oxygen dissociation curve to cause substantial decrease in the oxygen content of haemoglobin(Hb) even with a slight fall in PaO₂. In order to improve oxygen uptake in the lung, oxygen dissociation curve that determine the oxygen content of the blood shifts to left due to respiratory alkalosis caused by hypoxia induced hyperventilation. At the tissue level oxygen dissociation curve shifts to right to facilitate oxygen release from Hb. This rightward shift is due to renal compensation for respiratory alkalosis and increase in level of 2, 3-diphosphoglycerate (2,3-DPG) concentration.²⁷

Erythropoiesis

Hemoconcentration occurs on exposure to high altitude. Within few days of high altitude stay, Hb level increases due to increased erythropoiesis due hypoxia mediated erythropoietin release from the kidney.²⁸ Increased oxygen content of the blood improves oxygen delivery. Variability in the degree of high altitude induced erythropoiesis is observed in different highland population. Environmental and genetic factors have been implicated for the same. Colorado residents and Andean highlanders exhibit significant erythrocytosis while Tibetan highlanders have minimal or no erythrocytosis.^{29,30} Presence of excessive cobalt as well as genetic factors have been attributed for this difference among Andean highlanders. Polycythemia with hematocrit beyond 60% has deleterious effect on cardiac output and microcirculation due to increased viscosity of the blood. Hypercoagulability with prothrombotic state due to high altitude has been implicated in the pathogenesis of high altitude pulmonary edema and thromboembolism.

Tissue Changes

In the face of decreasing driving pressures observed in high altitude dwellers, many structural and metabolic changes occur to improve oxygen delivery and its utilization. These changes include: levels of myoglobin, cytoglobin, erythropoietin, neuroglobin and enzymes involved in oxidative phosphorylation.³¹

BENEFITS OF HIGH ALTITUDE

In the ancient text- 'Kumarasambhava' by the famous poet Kalidas, Himalayan mountains are described as a treasure house of innumerable precious stones, minerals, important herbs, trees, plants, creepers with delightful flowers; as the abode of the Siddhas, Ascetics, Yakshas, Kinnaras, Kiratas and various types of animals and birds; as the source of the Ganga and several other rivers. Undoubtedly Himalayan ranges have been a great treasure of knowledge and strength. Long term residents of Tibetan plateau have adapted very well to high altitude by exhibiting many beneficial physiological responses. Some of the beneficial effects of high altitude residence are enumerated below:³²⁻³⁴

- Increased ventilation rate
- increased red cell mass and hematocrit
- Increased red cell mass and hematocrit
- Muscles extract more oxygen
- Increased cardiac output
- Decreased cardiovascular mortality
- Increased basal metabolic rate
- Decreased air pollution and hypoallergenic conditions
- Better bronchial asthma control
- Reduced appetite
- Weight loss – reduced levels of obesity
- Better glucose metabolism
- Lower free radical injury at cellular level
- Delayed aging
- Increased longevity

ILL EFFECTS OF HIGH ALTITUDE

Sudden ascent to high altitude and stay there without adaptation is risky with high susceptibility to high altitude associated illnesses such as Acute Mountain Sickness(AMS), High Altitude Cerebral Edema(HACE) and High Altitude Pulmonary Edema(HAPE).^{21,35} Their frequency increases with increasing altitude. Thus height of stay matters so also rate of ascent, physical conditioning and associated morbidity, besides individual susceptibility. Young, obese and old are vulnerable. There are no specific markers to predict susceptibility but those with poor hypoxic ventilatory response(HVR) are at greater risk.

Acute high altitude illnesses respond to oxygen and descent to lower altitude. These conditions have several overlapping features. They can be prevented by avoiding undue physical exertion, gradual ascent, acclimatization and drug prophylaxis. Incidence varies from 9% to 70% among different population such as trekkers, skiers and Armed Forces personnel. Altitude-related exposure to cold may also contribute to illness. High altitude illnesses,

often pose serious challenges to health care system since prompt therapy is difficult to arrange due to lack of adequate medical facilities at the location of occurrence and hurdles in evacuating such cases to lower altitude where treatment facilities are available. Among altitude related acute illnesses, HAPE and HACE are serious conditions and can be fatal with mortality approaching 30%.³⁶⁻³⁸

High Altitude Headache

High Altitude Headache (HAH) is very commonly reported among those who are inducted to high altitude and is attributed to increased water loss with hyperventilation, overexertion and insufficient energy intake. Hypercapnia may also contribute by cerebral vasodilation.³⁹ Treatment consists of adequate hydration and analgesics for symptomatic relief.

Acute Mountain Sickness (AMS)

AMS is the commonest altitude sickness characterised by frontal headache, fatigue or weakness, dizziness or light headedness, nausea or vomiting, anorexia and difficulty in sleeping, occurring 4 hours to 36 hours of altitude exposure. Symptoms frequently occur on the first day and are severe in the morning after the first night stay at high altitude.

Incidence of AMS is altitude and time dependent affecting 22% to 70% of sojourners.⁴⁰ Rapid ascent to higher altitude affect the most.²¹ The exact pathogenesis is not clear. Cerebral vasodilatation, cerebral edema, changes in brain volume, raised intracranial pressure and hypoventilation have been implicated in the pathogenesis of AMS.^{41,42}

Symptoms are nonspecific and AMS can be mistaken for viral illness, poor sleep, intense exercise, jet lag, alcohol intake, carbon monoxide poisoning, dehydration and dyselectrolyemia. There are no specific clinical findings. Few crackles over lungs, peripheral edema and low oxygen saturation in some cases have been observed. Mental status as well as neurological examination is normal in AMS and the presence of abnormal mental status and or neurological finding suggests HACE which is a serious condition. Severity of AMS can be assessed by the Lake Louise Symptom Score Questionnaire (Table 2).⁴³

AMS is a self-limiting illness and recovery from it is expected after three days. In serious cases recovery takes longer. Treatment consists of supplemental oxygen through nasal prongs or face mask, rest and analgesics for relief of headache. Acetazolamide, a carbonic anhydrase inhibitor is widely used in the dosage of 250 mg twice day for three days in the treatment of progressive and severe AMS.⁴⁴ Dexamethasone can be used in a remote location in severe cases where rapid evacuation is not possible and descent is undertaken by keeping the subject ambulatory. Descent to lower altitude is required in few severe cases having progressive symptoms. A descent of about 300 meters can improve symptoms. Treatment inside a portable hyperbaric chamber is recommended in severe cases and in those cases where descent is not possible nor oxygen is available for therapy (Figure 4).⁴⁵

Table 2: Lake Louise Symptom Score Self Report Questionnaire. For assessing severity of AMS

Symptom	Severity	Point
Headache	No headache	0
	Mild headache	1
	Moderate headache	2
	Severe headache	3
Gastrointestinal	No gastrointestinal symptoms	0
	Poor appetite or nausea	1
	Moderate nausea or vomiting	2
	Incapacitating	3
Fatigue or weakness	Not tired or weakness	0
	Mild fatigue/weakness	1
	Moderate fatigue / weakness	2
	Incapacitating	3
Dizziness/light headedness	Not dizzy	0
	Mild dizziness	1
	Moderate dizziness	2
	Severe dizziness, incapacitating	3
Difficulty of sleeping	Slept as well as usual	0
	Did not sleep as well as usual	1
	Woke up many times, poor night's sleep	2
	Unable to sleep	3

*Score of > 4 AMS ** Score >10 severe AMS requiring immediate intervention

Inside these hyperbaric chambers, a pressure up to 2 psi and FIO₂ of 0.21% with low CO₂ can be maintained by ensuring sufficient gas flow by using a foot pump to simulate benefits of 2000 feet to 5000 feet descent.⁴⁶

High Altitude Cerebral Edema(HACE)

It is serious condition, potentially fatal having features of altered mental status or ataxia in a person with features of acute mountain sickness.⁴¹ In cases of HACE, there is gross cerebral edema (unlike mild edema seen in AMS), markedly elevated Intracranial pressure and micro haemorrhages in the brain. Ataxia can be demonstrated by heel to toe walking on a straight line or by positive Romberg sign.^{47,48} AMS is incapacitating and may be associated with global neurological dysfunctions such as papilledema, visual changes, aphasia, cranial nerve palsy, hallucinations, seizures, paraesthesia, clonus, bladder dysfunction.⁴⁹ It mimics many other causes of encephalopathy and gradual onset with global neurological dysfunction in a case of AMS prompts the

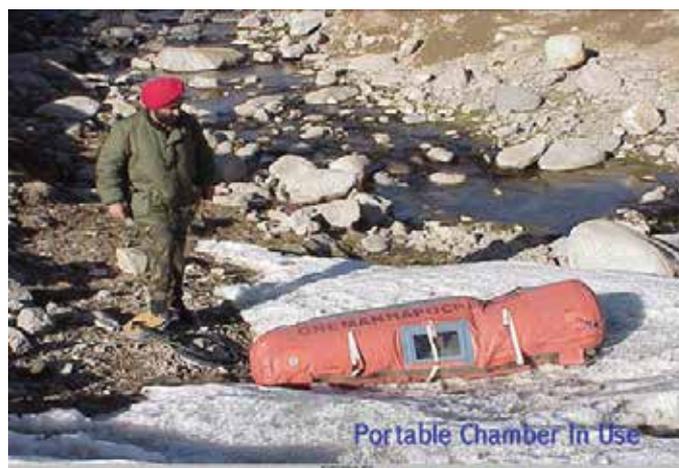


Fig. 4: Portable hyperbaric chamber with foot pump

diagnosis of HACE. Presence of somnolence, stupor and changes in pupillary responsiveness indicate severe disease with poor outcome. Some cases may have pulmonary edema.

Treatment consists of oxygen supplementation, hyperbaric therapy, descent to lower altitude of more than 1000 meters and use of dexamethasone. Oxygen should be given and it produces beneficial effect equivalent to 300 meters descent for every 1% increase in inspired oxygen above 21%. Hyperbaric therapy using portable chamber is a temporizing measure awaiting descent to lower altitude and the beneficial effects of hyperbaric therapy are slow to develop (Figure 4).^{37,45} Keeping the patient in hyperbaric chambers is useful as it improves symptoms and buys time for arranging descent. Emergency therapy with intramuscular administration of dexamethasone (4-8mg) is recommended in severe cases to reduce cerebral edema. This drug can be repeated once in every 6 hours.^{35,41}

High Altitude Pulmonary Edema(HAPE)

High Altitude Pulmonary Edema is a form of non-cardiogenic pulmonary edema affecting people after ascent to altitude usually above 2700 meters.⁵⁰ It can occur at altitudes as low as 2200 meters. Generally, it develops 2 days to 4 days after arrival at high altitude in other wise young and healthy individual who has climbed too fast or exerted on arrival.⁵¹ The incidence is from 0.25 % to 15 %, depending upon the altitude being inducted to and speed of ascent.^{21,35} Late onset HAPE is a new entity documented in Ladakh with manifestations of HAPE occurring 7 days to 65 days after the induction to high altitude.

The incidence of HAPE increases with increase in altitude and rate of ascent. Induction to high altitude by air than by road predisposes to higher risk especially if altitude is greater than 11,000 feet. Individual susceptibility varies and occurrence of recurrent attacks has been reported in the susceptible individuals. Pre-existing common cold and respiratory tract infection as well as unaccustomed physical exertion are risk factors. Re-inductees with previous history of HAPE are at a greater risk of recurrence. Some develop HAPE at a particular altitude on repeated ascents to that altitude only but not at a lower

altitude. Highlanders who descend to sea level and return back are also vulnerable.

Pathogenesis of HAPE is attributed to hypoxia induced exaggerated uneven pulmonary vasoconstrictor response.³⁵ This results in hypo-perfusion of constricted vessels while permitting hyper-perfusion of less constricted pulmonary vessels. This augmented pulmonary pressure and flow cause stress failure of capillary endothelium leading to leaky membrane and extravasation of fluid in to pulmonary interstitium and alveoli.⁵² Thus the events leading to HAPE are exaggerated non-homogenous pulmonary vasoconstriction, over perfusion of some regions of the pulmonary vascular bed, increased pulmonary capillary pressure, stress failure of pulmonary capillaries and leakage of alveolar fluid across capillary endothelium. Augmented sympathetic activity, increased levels of endothelin-1 and decreased levels of nitric oxide (NO) have been implicate in the pathogenesis. HAPE is also considered as a form of neurogenic pulmonary

edema due to sympathetic mediated venous constriction. Role of nitric oxide(NO) is supported by the beneficial clinical response to phosphodiesterase-5 inhibitors. Role of Inflammation in the pathogenesis is suggested by the pre-existing cold and upper respiratory infection seen in large number of patients with increased levels of C-reactive proteins and other inflammatory markers. In addition, various kinins have been identified in the edema fluid that are likely to increase permeability and recruit leukocytes.⁵³

Patients of HAPE may have symptoms of AMS initially before becoming breathless. They may have cough which is initially dry later becoming productive and frothy and pink. Examination reveals tachycardia, tachypnea, central cyanosis and inspiratory crackles over lung fields. As severity of HAPE increases, there is worsening of breathlessness and tachycardia and the inspiratory crackles become diffuse and bilateral with development of accentuated pulmonary component of 2nd heart

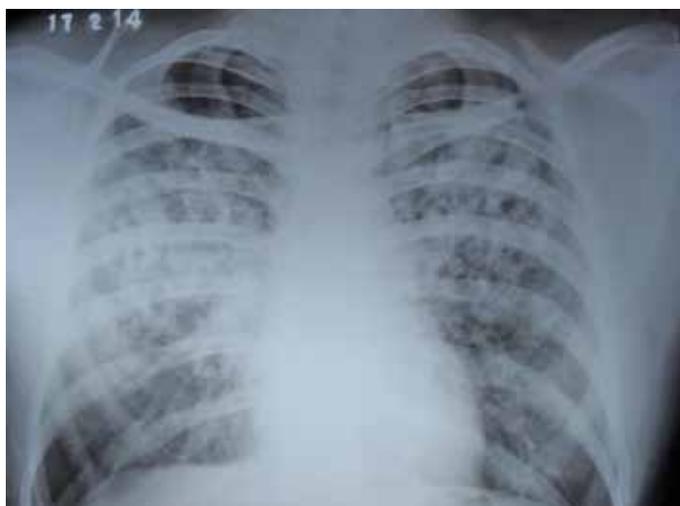


Fig. 5: Alveolar opacities BMZ & BUZ of lung fields



Fig. 6: CT Chest: Patchy alveolar opacities over right lung

Table 3: Medications for the Prevention and Treatment of Altitude Illness

Drug	Indication	Dose	Contraindication
Acetazolamide	Prevention of AMS	125 mg twice daily	Liver disease Avoid in CKD with GFR less than 10 ml/minute
	Treatment of AMS	250 mg BD	
Nifedipine	Prevention of HAPE	20-30 mg sustained release(SR) BD	Caution when in use with other antihypertensives; sudden drop in BP when used sublingually.
	Treatment of HAPE	20-30 mg SR BD	
Dexamethasone	Prevention of AMS	2mgQID/4mg BD	Avoid in peptic ulcer,Diabetetes.
	Treatment of HACE	8mg followed by 4 mg 6 hourly	
Tadalafil	Prevention of HAPE	10 mg BD	Liver disease Child's class C Dose adjustment in CKD with GFR less than 50ml/minute
	Treatment of HAPE	Role not established	
Sildenafil	Prevention of HAPE	50 mg 8 hourly	Liver disease Child's class C Dose adjustment in CKD with GFR less than 50ml/minute
	Treatment of HAPE	Role not established	
Salmeterol	Prevention of HAPE	125 microgram BD	Avoid concurrent use of beta blockers and in CAD
	Treatment HAPE	Role not established	

262 sound and features of right heart failure. HAPE may be unilateral in early or mild HAPE, usually involving right middle lobe. Pulse oximetry is a useful tool to document hypoxia and to monitor response to therapy. Oxygen saturation is inappropriately reduced and is much lower in severe cases. In a study of HAPO patients at an altitude of 4559 meters, observed values for SaO₂ was 48± 8% and for PaO₂ 23± 3 mm Hg as against healthy control values of 78±7% and 40±5mm of Hg respectively.⁵⁴ X-ray chest and computed tomography reveal patchy alveolar opacities (Figures 5 & 6). Echocardiography reveals evidence of pulmonary hypertension. In HAPE both pulmonary wedge pressure and cardiac size are normal.⁵⁵

Prevention

Drug Prophylaxis - in those who have experienced HAPE before, use of nifedipine prophylactically (slow-release formulation 20 mg twice daily prior to ascent, then three times daily) reduces the incidence of HAPE.⁵⁶ Nifedipine is a pulmonary vasodilator that causes smooth muscle relaxation with fall in pulmonary pressures. The drug appears to be ineffective in preventing AMS. Prophylactic use of an inhaled β-agonist may reduce the risk of HAPE.⁵⁷ Medications for the prevention and treatment of Altitude Illnesses are shown in the Table 3.^{35,41,44,56-59}

Acclimatization

High altitude illness can be prevented by acclimatization by means of gradual ascent and physical activity after initial rest on induction to high altitude(60,61). It is recommended to ascend 300-350 meters per day at altitudes above 2700 meters (sleeping altitude). Acclimatization schedules followed in high altitude areas are as under:

Stage I: 9000-12000 feet

- Day 1 & 2: Rest
- Day 3 & 4: Walk 1.5-3 km, avoid steep climbs
- Day 5: Walk up to 5 km
- Day 6: Walk up to 5 km. Climb 300m

Stage II: 12000-15000 feet

- Day 1 & 2: Walk up to 1.5-3 km, avoid steep climbs
- Day 3: Walk up to 3 km, climb up to 300m
- Day 4: Climb 300m without equipment.

Stage III: 15000-18000 feet

- Day 1 & 2: Walk up to 1.5-3 km, avoid steep climbs
- Day 3: Walk up to 3 km, climb up to 300m
- Day 4: Climb 300m without equipment

Absence from high altitude(Re-inductees)

- Less than ten days acclimatization not required
- More than 28 days: Complete acclimatization

10 to 28 days

- Day 1 & 2: Rest except short walk
- Day 3: Walk at slow pace 1-2 km, avoid steep climb

- Day 4: Walk for 1-2 km, climb up to 300m.

Treatment

Apart from rest and supplemental oxygen immediate descent to lower altitude is vital for a better outcome and an early recovery. Patient should be evacuated to lower altitude as soon as possible since an immediate descent of 500 meters to 1000 meters can hasten recovery. Oxygen therapy is the mainstay of therapy. High flow rates of oxygen through face mask/ nasal prongs to ensure FIO₂ of 40% is given to keep arterial oxygen saturation of greater than 90% and oxygen therapy is continued till one becomes asymptomatic and pulse rate normalises. In remote locations where descent is not possible, therapy with 10 mg nifedipine per orally can be initiated with careful monitoring for hypotension and if no significant hypotension occurs, then the drug can be repeated after 30 minutes. Though many pulmonary vasodilators have been tried, nifedipine remains the drug of choice. The use of hyperbaric chamber especially portable that simulates conditions of lower altitudes is recommended and is quite effective in managing HAPE when urgent descent is not possible. Keeping the patient inside a portable hyperbaric chamber achieves the benefits of simulated descent of 1500 meters to 1800 meters. In a hospital setting, larger stationary hyperbaric chambers are used. The use of CPAP can improve oxygenation.

Sub-Acute Mountain Sickness(SAMS)

This condition has been described among Indian soldiers who stayed for more than 10 weeks in high altitude between 5800 to 6700 meters and presenting with features of pulmonary hypertension and right heart failure due to exaggerated hypoxic pulmonary vasoconstriction.⁶² Treatment is evacuation to lower altitude and supportive therapy.

Chronic Mountain Sickness(CMS)

This condition also known as Monge disease was described in 1920s by Carlos Monge in high-altitude residents of the Andes who presented with polycythemia.⁶³ It is characterized by a triad of polycythemia, hypoxemia and impaired mental function among long term residents (> 1 year). These cases have extreme polycythemia, with Hb and haematocrit values as high as 23 g/dL and 83% respectively. They have lower oxygen saturation and hypoxic ventilatory response with relative hypercapnia. They develop pulmonary hypertension and right ventricular enlargement. Features include headache, dizziness, somnolence fatigue, irritability, impaired concentration, loss of mental acuity, depression and even hallucinations.⁶⁴ They have poor exercise tolerance; though exertional breathlessness is uncommon.⁶⁵ They also have clubbing and cyanosis.

Treatment consists of descent and stay at lower altitude, periodic phlebotomy, diuretics and respiratory stimulants.⁶⁴ Descent to sea level is the definitive treatment. However, for those who wish to remain at altitude, phlebotomy and administration of supplemental oxygen are beneficial. Phlebotomy improves many of the

neuropsychological symptoms, and in some patients, pulmonary gas exchange and exercise performance have also improved. ACE inhibition has been found to be effective and safe to ameliorate altitude polycythaemia while also in reducing proteinuria.⁶⁶ Role of drugs such as medroxyprogesterone, acetazolamide and sildenafil have not been established. Acetazolamide may be useful in improving oxygen saturation during sleep. Medroxyprogesterone has been tried with some success.

High Altitude Pulmonary Hypertension

In this condition there is pulmonary hypertension (mean pulmonary artery pressure >30 mm of Hg and systolic pulmonary artery pressure > 50 mm of Hg) with cor pulmonale without excessive erythrocytosis (Hb <21 g/dl in men and <19 gm/dl in women) among long term residents of high altitude.⁶⁷ They have overlapping features of subacute mountain sickness and CMS. Treatment of this condition is descent to lower altitudes and supportive.

HIGH ALTITUDE ILLNESSES UNRELATED TO ACCLIMATIZATION

There are several respiratory conditions that are influenced by high altitude exposure but their occurrence



Fig. 7: X-ray chest showing wedge opacity RLZ with blunting of CP angle and elevated diaphragm

is unrelated to acclimatization.⁶⁸ These conditions include: Chronic Obstructive Pulmonary Diseases (COPD), Bronchial Asthma, Interstitial Lung Disease (ILD), Sleep Apnea, Pulmonary Hypertension and Pulmonary Thromboembolism.

Chronic Obstructive Pulmonary Disease (COPD)

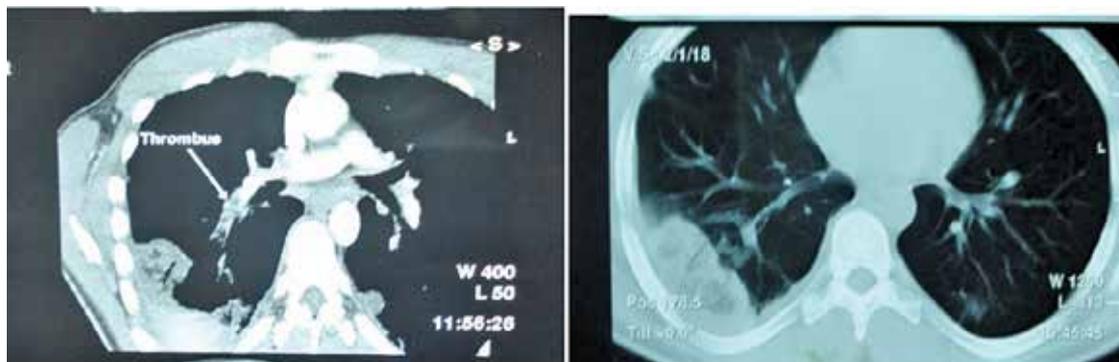
Incidence of COPD is lower in high altitude. Those with pre-existing COPD become more hypoxemic at high altitude.³² These cases should undergo detailed evaluation before induction to high altitude and to be assessed for therapy with O₂ supplementation.⁶⁹ If PaO₂ is found to be <50-55 mm Hg, travel to high altitude if deemed necessary can be undertaken with adjusted supplemental O₂ therapy and pulse oximetry monitoring. Pneumothorax becomes worse at high altitude and those with bullae and emphysema should not travel to high altitude. All cases of COPD should be evaluated for the same before they are advised for travelling to high altitude.⁶⁸

Bronchial Asthma

High altitude stay has been found to be beneficial to asthma patients due to lower ambient temperature, humidity, allergen load and air density. Decreased airway resistance improves airflow and asthma control.⁷⁰ Ultraviolet radiation exposure at high altitude has an immunomodulatory effect. However, severe hypoxia, hypocapnea and cold air prevalent in high altitude can have adverse impact on asthma control by aggravating bronchial hyper-responsiveness. Well controlled asthmatics can travel up to altitude of 5000 meters provided they continue baseline medications and carry ample rescue medications and steroids. Those with severe asthma are advised against travel to high altitude. However, some uncontrolled and refractory cases can benefit from high altitude sojourn undertaken with proper medication and supervision due to aforementioned beneficial effects of high altitude on asthma control.

Interstitial Lung Disease: Exposure to high altitude worsens dyspnea, hypoxemia and pre-existing pulmonary hypertension.⁷¹ These cases have poor exercise tolerance. Treatment is essentially supportive and supplemental oxygenation if PaO₂ < 50-55 mm Hg.

Pulmonary Thromboembolism & thrombosis: High altitude is a prothrombotic state with increased risk of thrombosis and pulmonary thromboembolism.⁶⁸ These



Figs. 8 & 9: CT Angio: thrombus in right lower pulmonary artery with pleural based consolidation

264 cases should be evacuated to lower altitude and managed on standard lines. Figures 7, 8 & 9 show thrombus in the pulmonary artery with pulmonary infarct in a high altitude inductee.

Pulmonary hypertension: Those with pre-existing pulmonary hypertension are at increased risk of HAPO, right heart failure and subacute mountain sickness. These cases should avoid travel in to high altitude. If travel becomes unavoidable then supplemental O₂ and nifedipine SR at 20 mg BD should be given during their stay in high altitude. Sildenafil/dexamethasone as an alternative to nifedipine can be given.

Obesity Hypoventilation Syndrome: Obstructive sleep apnea improves but central sleep apnea worsens on exposure to high altitude.⁷² The beneficial effect of lower incidence of obstructive apneas is offset by increase in central apneas. Those who travel to high altitude should use Continuous Positive Airway Pressure (CPAP) ventilation. Due to hypobaric conditions, set CPAP is not delivered by the portable CPAP machine in the absence of pressure compensating features. In this situation higher pressure is needed to deliver set pressure by the CPAP machine to produce relief from symptoms.

CONCLUSIONS

High altitude regions in the world are increasingly being explored and have become permanent abode for about 2% of world's population. High altitude is an alien environment of extreme hypoxia and hypothermia with low barometric pressure and intense exposure to ultraviolet radiation. Respiratory system vital for oxygenation of tissue plays an important role in adaptation to high altitude. Maladjustment to high altitude conditions leads to various illnesses that are acute, subacute and chronic in nature. Majority of them affect respiratory system. Treatment of these conditions is essentially the management of high altitude related hypoxia that can be best achieved by evacuating them to normobaric normoxic condition. Prophylactic medication and strict adherence to acclimatization schedule significantly reduce risks of altitude related acute illnesses occurring among lowlanders who ascend to high altitude. Those long term residents who acclimatize and adapt well are sure to harvest several physiological benefits. In the human evolution, higher regions of the world have inspired many to conquer nature by reaching to greater heights. High altitude regions of the world not only pose physiological challenges but also provide the milieu for the mankind to evolve to higher levels.

Maladies are the tragedies of time
Affecting one who is lame
In this evolutionary game
Conquer time to be in infinite frame
Are mountains really tall
From the star looks very small
In inverted space a narrow pit

They are big for tiny a lot

To become the master through their hat.

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