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# Cardiovascular Response to High Altitude Hypoxia

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**Abstract.** Normal and abnormal cardiovascular response to high altitude (HA) hypoxia were studied in 98 healthy subjects and in 15 patients with HA pulmonary oedema (HAPO) and acute mountain sickness (AMS) at an altitude of 3,658 m. The healthy sea level (SL) residents showed marked blood volume changes during the first week with pulmonary hypotension and depression of left ventricular (LV) performance and physical work capacity (PWC). The HA natives, however, had better LV performance and PWC indicating a better adaptation to HA hypoxia. HAPO subjects showed evidence of severe pulmonary hypertension with normal left atrial pressures but the exact mechanism of this condition is still not clear. AMS subjects showed no circulatory abnormalities but had relative hypercapnia and severe hypoxemia suggesting that AMS may be caused by relative hyposensitiveness of the respiratory centre to hypoxia or hypercapnia.

## 1. Introduction

A sea level (SL) resident arriving at high altitude (HA) is exposed to decreased atmospheric pressure and proportionate reduction in partial pressure of oxygen in the inspired air. This leads to arterial hypoxemia which stimulates carotid and aortic chemoreceptors to cause hyperventilation resulting in elimination of $CO_2$. Thus the SL resident exposed to HA, encounters not only acute hypoxia but also hypocapnia and respiratory alkalosis resulting in numerous circulatory alterations. The acute and chronic effects of high altitude on the cardiovascular system of normal men were studied on a group of healthy SL residents and a group of permanent residents of HA. Few patients who developed high altitude pulmonary oedema (HAPO) and acute mountain sickness (AMS) at HA were also studied to determine the abnormal response of HA hypoxia in man. A few communications based on this work have been reported earlier[1-6].

## 2. Material and Methods

73 healthy, physically active male SL residents (mean age 23 years) and 25 HA natives (mean age 24 years) from the Armed Forces volunteered for the study. The SL residents were first studied at SL and subsequently air lifted to an altitude of 3,658 m and restudied between 1-10 days of arrival and again after 22 months of intermittent stay at that altitude under identical conditions of temperature and procedures. The HA natives were studied only once at HA.

A routine right and percutaneous left heart cathetrization were performed in these subjects in a resting postabsorptive state. Intracardiac pressures were measured using Statham strain guaze P23 AA transducers and a photographic recorder. Total blood volume (TBV) was estimated by Evans Blue dye and pulmonary blood volume (PBV) by the technique of Dock *et al*[7]. The cereberal blood flow (CBF) and coronary flow (CF) were determined by the method of Kety and Schmidt[8] and peripheral blood flow (PBF) by venous occlusion plethysmography. Non-invasive techniques of systolic time intervals and transthoracic electrical impedance (TEI) to determine the thoracic fluid volume changes were also employed in some subjects by the methods described by us earlier [9–10]. Maximal oxygen uptake ($VO_2$ max) was determined by the standard method on an electrically braked bicycle ergometer (Elema Scholander EM 369) i. e. establishment of levelling off point for $VO_2$ with increasing interrupted work loads. 10 subjects who developed HAPO and five with AMS were also studied at rest utilising the same methodology at HA.

## 3. Results

### 3.1 *Normal Response to HA Hypoxia*

#### 3.1.1 *Acute Response in SL Residents*

##### 3.1.1.1 *Blood Volume Shift*

The TBV did not significantly alter during the first six days at HA but the PBF decreased significantly (Fig. 1). During exercise at SL, the PBF increased significantly but at HA, the PBF either increased slightly or actually decreased on day 3 and 4. The resting PBV showed a marked increase (83 per cent) especially on day 3 and 4 and approached normal SL values by day 6. The central blood volume (CBV) also showed similar changes though less in magnitude. The transthoracic electric impedance also showed a significant decrease at HA especially during the first three days. CBF measured as 100 g of brain tissue increased significantly within the first two days after which it decreased gradually and approached SL values by day 6. CF per 100 g of left ventricle, however decreased significantly ($p.<01$) during the first four days at HA. The myocardial $O_2$ consumption also decreased in a similar fashion. Although, arterial lactate content increased at HA, the myocardial lactate extraction decreased.

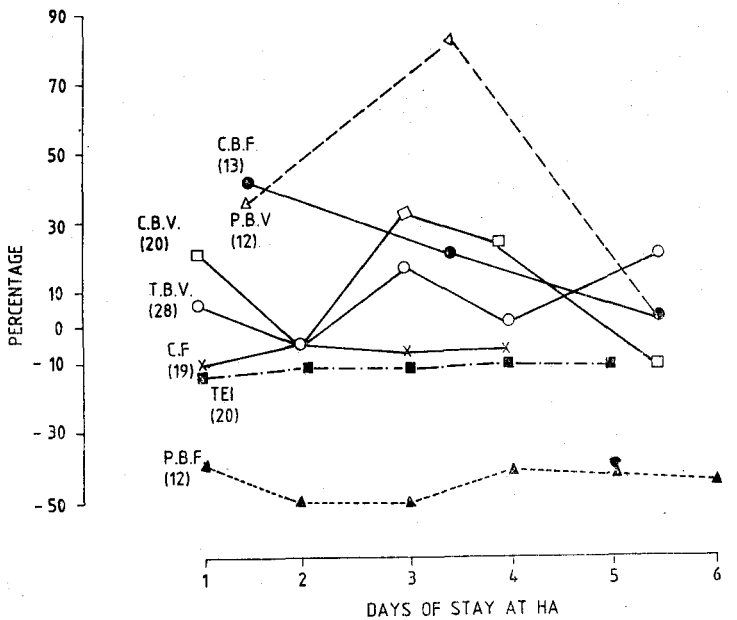


**Figure 1.** Blood volume shifts in sea level (SL) residents during first six days of exposure to high altitude (HA) hypoxia. While the total blood volume (TBV) is not altered significantlly, the cerebral blood flow (CBF), pulmonary blood volume (PBV), and central blood volumes (CBV) increased but the coronary (CF), peripheral blood flow (PBF) and transthoracic impedance (TEI) decrease. Values within parentheses represent the number of subjects.

### 3.1.1.2 *Pressure/Flow*

The heart rate increased significantly during the first two days at HA in SL residents. The cardiac index (CI) and stroke index (SI) were not significantly altered. The resting pulmonary arterial systolic pressure (PAP) increased by 14 per cent within two days of altitude exposure, but the maximum increase was seen on day 3 and 4 (+42%). There were marked individual variations in increase in PAP. During exercise, the PAP increased markedly but 100 per cent $O_2$ reduced the elevated pressures to SL values (Fig. 2). The systemic arterial, right left atrial and pulmonary arterial wedge pressures did not significantly change during the first six days at HA.

### 3.1.1.3 *Cardiac Function and Physical Work Capacity*

Non-invasive measurements of systolic time intervals revealed a significant prolongation of pre-ejection period (PEP), abbreviation of left ventricular ejection time (LVET) and significant increase in PEP/LEVT ratio at HA. The maximum changes were seen on day 2 and 3. During submaximal and maximal exercise, the PEP/LVET ratios further increased. Simultaneously, the $VO_2$ max (reflecting physical work capacity) decreased significantly in SL residents at HA during the first 10 days, decreasing from a mean of 53.9 ml/kg at SL to 39.9 ml/kg at HA ($p < .01$) (Fig. 3).

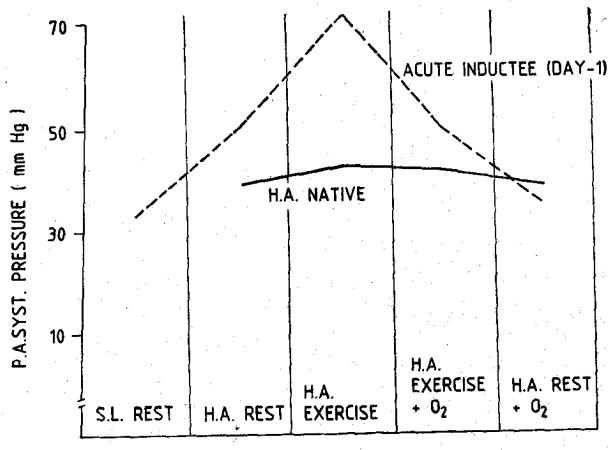


**Figure 2.** Effect of HA hypoxia and $O_2$ on pulmonary arterial (PA) pressures. Acute exposure to HA increased the PA pressure in the SL resident, and exercise further increased it. 100% $O_2$ inhalation reverted the pressures to SL values. In the HA native, however, the $O_2$ inhalation had no significant effect on elevated PA pressure.

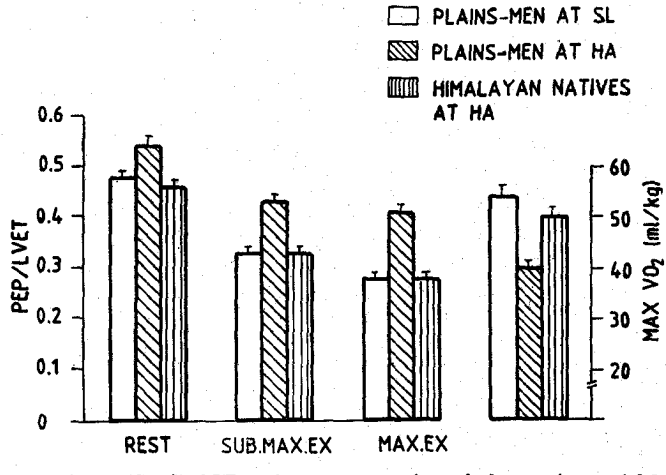


**Figure 3.** PEP/LVET ratios at rest and graded exercise and Max $VO_2$ at SL and HA. The PEP/LVET ratio was significantly higher (indicating depressed left ventricular performance) in SL residents at HA especially during max exercise. The $VO_2$ max was similarly decreased. The HA natives had lower PEP/LVET ratios and higher $VO_2$ max at HA.

### 3.1.2 *Response of Prolonged Stay at HA*

13 SL residents stayed at altitudes varying between 3,658 to 4,300 m intermittently for 22 months, the duration of their last continuous stay varying from between 8 to 52

weeks. They were studied for the third time at an altitude of 3,658 m. The haematocrits increased in these subjects and the TBV decreased. The heart rate was similar to SL values. The PAP increased further. The PBV which had increased during day 3 and 4 at HA normalized by day 6, again increased by 47 per cent but CBV was not altered. The CBF values were similar to SL values. The CI and SI were slightly reduced. The PBF, which had decreased during first six days at altitude, tended to revert to SL values.

3.1.3 *High Altitude Residents (Himalayan Natives)*

The Himalayan natives showed no polycythemia. Their PBV, PAP and CBF increased in comparison to SL residents and the CF and myocardial $O_2$ consumption were reduced. The myocardial extraction coefficient of lactate was also reduced. Inhalation of 100 per cent oxygen did not decrease the elevated PAP, unlike in SL residents at HA (Fig. 2). The transthoracic electric impedance was reduced and the PEP/LVET ratio did not increase either at rest or during submaximal or maximal exercise. Their $VO_2$ max (mean 50.0 ml/kg) was significantly higher ($p<.01$) than SL residents at HA (mean 39.9 ml/kg).

3.2 *Abnormal Cardiovascular Response to HA Hypoxia*

3.2.1 *High Altitude Pulmonary Oedema (HAPO)*

Ten patients with HAPO were studied within 6-24 hours after the onset of pulmonary oedema while they were still acutely ill. They showed evidence of tachycardia and reduced stroke volume but the cardiac index was normal. The TBV, CBV and PBV were normal in the acute stage though in convalescents of HAPO, the PBV increased. They had marked reduction of PBF and TEI. The PAP markedly increased in all patients but the pulmonary arterial wedge and left atrial pressures were within normal limits. In addition these patients had increased alveolar arterial $O_2$ tension gradients.

3.2.2 *Acute Mountain Sickness (AMS)*

Haemodynamic studies were done in five patients with AMS. They showed a reduction in TBV but the other parameters like heart rate, cardiac and stroke indices, PAP, CBV, CBF and PBF were not different from the SL residents at HA. They had, however, higher level of Pa $CO_2$ and lower $PaO_2$ values as compared to normal subjects at HA.

## 4. Discussion

It is apparent from the data presented that there occurs a marked blood volume shift during acute exposure to HA hypoxia. While the TBV remains unchanged, the PBF and CF diminish significantly and the PBV, CBV and CBF concomitantly increase. A decrease in transthoracic electrical impedance would also indicate an increase in the

thoracic fluid volume during acute altitude hypoxia[11-13]. It was further possible to correlate the marked increase in CBF in subjects with severe headache and a marked decrease in transthoracic impedance with symptoms of marked dyspnoea. There was a marked individual variability in the response of PAP during acute hypoxia. In a few subjects, the increase was more than 100 per cent while in some others, the PAP was hardly altered. Exercise, however, caused a consistent and marked elevation of pulmonary pressures in all subjects. The rise in PAP can be attributed to hypoxic vasoconstriction, since 100 per cent $O_2$ inhalation decreased the pressures to normal values in SL residents. Mild exercise also caused a significantly different peripheral vascular response in acute altitude hypoxia. Unlike at SL, where exercise resulted in an increase in PBF, the flow actually decreased during exercise on day 3 and 4 at high altitude. The incidence of high altitude pulmonary oedema is highest[14] and the resting PBV and the transthoracic impedance lowest, during this period (viz. day 3 and 4 at altitude). It is probable that during exercise a large amount of blood goes from the periphery to the pulmonary circuit and this may precipitate high altitude pulmonary oedema in certain susceptible subjects.

The response of CBF and CF to acute high altitude hypoxia may appear paradoxical because hypoxia of short duration causes coronary vasodilatation and hypocapnia is a strong cerebral vasoconstrictor[15,16]. However, similar findings have been reported by others. Severinghaus *et al*[17] showed an increase in CBF during acute HA hypoxia and Grover *et al*[18] studying three lowlanders observed a marked decrease in CF after 10 days of stay at an altitude of 3,100 m. It would thus appear that a prolonged hypoxia of more than 24 hours elicits different responses in cerebral and coronary circulation as compared to short lived hypoxia. Decreased myocardial lactate extraction would suggest the presence of anaerobic myocardial metabolism during acute high altitude hypoxia in our subjects. Grover *et al*[18], however, were not able to demonstrate any decrease in lactate extraction in their three subjects although one of the subjects did have decreased lactate utilization. If we determine the left ventricular (LV) performance by the non-invasive measurements of PEP/LVET which has been shown to be a reliable index of LV function by numerous investigators[19-21], it is apparent that acute exposure to high altitude hypoxia causes a depression of LV performance in normal young healthy subjects. Depression of myocardial contractility has also been demonstrated in experimental animals at high altitude[22] and in man during graded exercise in acute hypobaric hypoxia[23]. During submaximal and maximal exercise at HA, there is a further reduction in LV performance as reflected by increase in PEP/LVET ratios unlike at SL where the LV function improves during exercise. The SL residents have a concomitant decrease in their physical work capacity (reflected by $VO_2$ max measurements) at HA. The depression of LV function seemed to correlate with decrease in $VO_2$ max at altitude. Depression of LV function during maximal exercise may thus be responsible for decreased physical work capacity at altitude. The reason for decreased LV performance during maximal exercise is not apparent from this study. However, severe exercise at HA has been reported to result in increased hypoxemia[24] and acidosis[25]. A combination of hypo-

xemia and acidosis may depress cardiac performance at HA as both these factors have been shown to have an additional effect in depressing cardiac function in experimental animals. Reduction in $VO_2$ max has also been reported by several other investigators at HA in proportion to level of altitude[26].

During prolonged intermittent stay at high altitude, the main adaptive processes appear to be development of polycythemia, normalization of heart rate and CBF, pulmonary hypertension and increase in PBV. The permanent residents of HA, however, do not show polycythemia which is seen in Peruvian Andes residents[27]. The reason for absence of polycythemia is not clear. It is possible that Himalayan natives are relatively anaemic due to some chronic worm infestation. However, this needs further exploration. TBV also is not increased unlike in residents of Peruvian Andes[27]. The HA residents have evidence of pulmonary hypertension with organic changes in the pulmonary vessels because oxygen inhalation does not lower pulmonary pressures in these subjects. The other adaptive processes appear to be the increase in PBV and CBF and decrease in PBF, CF and myocardial $O_2$ consumption. They also have evidence of anaerobic cardiac metabolism because the lactate extraction is decreased. Reduction in CF has also been reported in residents of Bolivian Andes by Moret et al[28] although they were not able to find evidence of anaerobic cardiac metabolism. The left ventricular performance evaluated by PEP/LVET ratio does not show any depression in HA natives unlike in the SL residents at HA either at rest or during maximal exercise. A better cardiac performance may be the reason for better physical work capacity in the HA natives compared to SL residents at HA.

Patients with high altitude pulmonary oedema have markedly raised PAP which has also been reported by other investigators[29,30]. However, no previous data except from our group[2] on simultaneous recordings of pulmonary artery wedge and left atrial pressure is available for comparison. The PBF is markedly reduced and the PBV is probably increased. Although, during the acute phase, the estimated PBV did not increase, but the technique employed by us measures only intravascular PBV and not the fluid leaked into the lungs. However, the PBV in HAPO convalescents increased. Therefore, it may be surmised that PBV increased in HAPO subjects. The exact mechanism leading to pulmonary oedema in the setting of pulmonary arterial hypertension in the absence of raised pulmonary artery wedge and left atrial pressure is not clear. Possible alterations of pulmonary capillary permeability because of hypoxia, may be present and many explain the high protein content of oedema fluid[31] and presence of red blood cells. On the basis of histopathological studies, Arrias-Stella and Kruger[32] suggested that a sudden rise of PAP (due to hypoxia and exercise in certain susceptible individuals) coupled with blood volume shifts from systemic to pulmonary circulation and simultaneous opening of special preterminal arterioles would increase the capillary hydrostatic pressure and may be responsible for oedema. No such vessels were, however, observed by Nayak *et al*[31] although Vishwanathan *et al*[33] demonstrated such vessels in the lungs of experimental animals with HAPO.

Patients with acute mountain sickness showed no significant cardiovascular abnormalities as compared to SL residents at HA except that the CBF tended to be higher in most patients. However, these patients show significant reduction of minute and alveolar ventilation, relative increase in arterial $CO_2$ tension and metabolic alkalosis. Even more striking is the evidence of significant hypoxemia with marked reduction of $O_2$ tension in the arterial blood, low $O_2$ saturation and marked widening of the oxygen tension gradients at the inspired air alveolar level and the alveolar arterial level. This suggests that the hypoxemia in these patients is due to abnormalities at two levels (a) reduced ventilation causing a greater than normal $O_2$ gradient between inspired air and alveolar air and (b) abnormalities of gas exchange at the alveolar and pulmonary capillary level responsible for a wide alveolar arterial $O_2$ tension gradient. Our data of blood gas and acid base analysis is different from that of Shields *et al*[34], who reported respiratory alkalosis and hypocapnia in such patients. It is possible they studied less severe cases. Since no obvious abnormalities of the chest cage were present, it was most likely the result of a depressed respiratory centre insensitive to a chemical drive generated by low Pa $O_2$ ar high Pa $CO_2$. No tests were however carried out to determine the relative sensitivity of respiratory centre to $CO_2$ or hypoxia in these subjects. However, Severinghaus *et al*[35] have reported that chronic mountain sickness is possibly caused by the hyposensitiveness of the respiratory centre to hypoxia. It is possible that individual variations in the sensitivity of the respiratory centre may ultimately be responsible for the variable intensity of symptoms suffered by persons exposed to HA environment.

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