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Exercise Responses to Metabolic Function on High Altitude Pulmonary Edema Susceptible Individuals

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ABSTRACT

The study was aimed to evaluate and compare resting and exercise induced metabolic responses between acclimatised high altitude pulmonary edema (HAPE) susceptible (HAPE-s) and HAPE resistance (HAPE-r) volunteers at sea level. A group of 14 Indian soldiers volunteered for this study, divided into two groups, (i) HAPE-s, with past history of HAPE [n_1 = 7; age = 33.3 ± 4.5 (M ± SD)] and (ii) HAPE-r, with prior history of repeated exposure to high altitude and without suffering HAPE [n_2 = 7; age = 31.9 ± 4.2 (M ± SD)]. Respiratory frequency (f_R), tidal volume ($\dot{V}_T$), minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), heart rate (HR) and respiratory quotient (RQ) were recorded on all the volunteers during resting and exercise conditions. Ventilatory equivalent for oxygen (EqO_2) and oxygen pulse (O_2P) were calculated. Significant differences were observed between HAPE-s and HAPE-r volunteers in f_{Rrest} (25.3 % higher), O_2P_{rest} (23.7 % lower), $\dot{V}_{Emax}$ (50.9% lower) (all P<0.05), f_{Rmax} (55.7 % lower), $\dot{V}O_{2max}$ (55.5 % lower), O_2P_{max} (34.2 % lower) (all P<0.01) and $\dot{V}CO_{2max}$ (42.1 % lower, P<0.001). Rest of the parameters did not show any significant differences between the study groups. The study revealed that resting and exercise induced metabolic responses of HAPE-r volunteers was better as compared to acclimatised HAPE-s volunteers at sea level.

Keywords: High altitude; Hypoxia; High altitude illness; HAPE; Exercise; Ventilatory function

1. INTRODUCTION

With the rapid improvement in transport and communication systems, an increasingly large number of people are going to high altitude for adventure and challenges such as touring, mountaineering, trekking and different mountain sports. Moreover lowland residents are also moving to high altitude for employment. Due to strategic reasons swift deployment of sea level or low altitude military personnel to high mountain regions has also become necessary for combat defence purposes. High altitude exposure affects human body because of low partial pressure of oxygen (hypoxia), severe cold, high wind and intense solar radiation. Due to acute *hypobaric hypoxia* in otherwise previously healthy individuals who visited high altitude may suffer from high altitude illness (HAI). High altitude induced pulmonary edema (HAPE) is one of the most ominous type of HAI. It is a kind of non-cardiogenic type of pulmonary oedema that develops in non-acclimatised persons after rapid ascent to[1] and/ or extreme physical exertion at an altitude above 2500 m. The primary causative factors for the development of HAPE are the altitude attained, speed and mode of ascent, amount of physical activity and above all degree of individual susceptibility[2,3]. Increased sympathetic activity via α-adrenergic efferent pathways[4] endothelial dysfunction, hypoxemia from a poor ventilatory response to hypoxia, uneven exaggerated hypoxia related pulmonary vasoconstriction[5] along with excessive-perfusion of certain regions of the pulmonary vascular bed and excessively elevated pressure in pulmonary artery and capillary are considered as crucial pathogenic factors for the development of this type of hydrostatic pulmonary oedema[6,7]. The excessively elevated pulmonary artery systolic pressure while exercising in both normoxic and hypoxic conditions[8] leads to mechanical injury or 'stress failure' of pulmonary capillaries[9], causing extravasation of high-molecular-weight proteins, erythrocytes, leukocytes (mostly alveolar macrophages) and inflammatory markers into the alveoli[10]. This stress failure causes vascular leakage in the lungs either by altering the structure of the capillary endothelium and alveolar epithelium by relaxing tight junctions between the cells and/ or by forming transcellular passage through vesicular channels[11]. It has been reported that decreased bioavailability of nitric oxide contributes hypoxia induced endothelial dysfunction in HAPE susceptible volunteers which in turn contributes enhanced hypoxic pulmonary vasoconstriction and finally development of HAPE[12].

Plenty of research articles are available on resting and exercise induced physiological function of HAPE susceptible (HAPE-s) and HAPE resistance (HAPE-r) volunteers at sea level and high altitude both[3,14,15]. But a systemic study concerning the metabolic functions of HAPE-s volunteers to whom HAPE had developed in spite of proper 6 day acclimatization is still limited to the best of our knowledge. The present study was therefore designed for a comprehensive

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evaluation and comparison of resting and exercise induced responses of metabolic function between acclimatised HAPE-s volunteers with acclimatised HAPE-r volunteers at sea level. Data from the present study might be helpful in understanding the pattern of metabolic responses during resting and exercise induced state of acclimatised HAPE patients at sea level.

2. MATERIAL AND METHODS

2.1 Subjects

This is a cross sectional study conducted at the DRDO-Defence Institute of Physiology and Allied Sciences, Delhi. Fourteen participants (N = 14), under 'Other Ranks' (ORs) category from Indian Army, participated in the present study. They were divided into two equal groups –

(i) HAPE susceptible (HAPE-s) (n_1= 7), are sojourners who suffered the disorder (radiographically detected) upon exposure to HA (~3500 m) and

(ii) HAPE resistance (HAPE-r), are the healthy volunteers, who posted at HA under similar conditions but did not suffer from the disorder (n_2 = 7).

All the HAPE-s volunteers had experienced more than two episodes of radiographically and clinically documented HAPE in spite of following proper acclimatization schedule (Army Order: 110/80). All the volunteers were non-smokers with no history or symptoms of any kind of clinical disorders except pulmonary edema in HAPE-s volunteers only. The Institutional Ethical Committee on Human investigation approved the entire study protocol. The purpose the present study and their role were elucidated to every volunteer. As per declaration of Helsinki individual written informed consent was obtained from the participants.

The participants were asked not to eat, drink or do any kind of vigorous physical activity at least 2 h before the onset of experiments. To normalie their heart rate to a steady state they were also allowed to take rest for a minimum period of 30 min.

2.2 Parameters

2.2.1 Anthropometric Measurements

Anthropometric parameters were assessed with light clothing and barefoot. The standing height was assessed with a stadiometer without shoes to the nearest 0.1 cm from sole of the feet to the vertex in erect body position. Using a digital weighing machine (ID150H, Delmar, India) body weight was measured in empty stomach and bladder. Body mass index (BMI) was calculated by using the following formula –

$$BMI = \frac{Weight\ (\text{kg})}{\left[Height\,(m)\right]^2}$$

2.2.2 Resting Metabolic Parameters

The resting metabolic parameters were taken in sitting condition using a PC based equipment set-up (K4b^2, COSMED, Italy). The parameters recorded were respiratory frequency (f_R), tidal volume ($\dot{V}_T$), minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and respiratory quotient (RQ). Heart rate (HR) was continuously recorded with a Polar HR belt (Polar Electro OY, T34, Polar), connected with K4b^2 system telemetrically. Ventilatory equivalent for oxygen (EqO_2) and oxygen pulse (O_2P) were also calculated.

2.2.3 Metabolic Parameters During Exercise Maximal

All the above mentioned metabolic parameters were also recorded during graded exercise protocol. Exercise was performed on a stationary bicycle ergometer (Monark-Ergomedic 828E, Monark Exercise AB, Sweden). Cycling protocol began with a light warm-up without any work-load followed by regular graded incremental work-load of 25 watts in every 2 min keeping the speed maintained at 50 rpm. Exercise continued with this protocol until a plateau of $\dot{V}O_2$ was attained or the participant could not paddle at the defined pace.

2.2.4 Statistical Analysis

Data was expressed as Mean ± SD and analysed using software, Statistical Package for Social Sciences (v21.0, SPSS, Inc., Chicago, IL, USA). The significance of difference between the means was analysed using two-tailed Student's t-test for small (n < 30) paired samples. The significance level was defined as $p<0.05$ (two-tailed).

3. RESULTS

Table 1 shows the anthropometric characteristics of HAPE-s and HAPE-r volunteers. No significant difference was observed in height, weight, BMI and BSA between the two groups. Resting metabolic parameters of the HAPE-s and HAPE-r volunteers are presented in Table 2. Resting respiratory frequency of the HAPE-s volunteers was significantly higher ($P<0.05$) than HAPE-r participants. Resting oxygen pulse HAPE-s participants was significantly lower ($P<0.05$) than HAPE-r volunteers. Resting tidal volume, ventilation, oxygen consumption, carbon dioxide output, ventilatory equivalent for oxygen, heart rate and respiratory quotient did not show any significant difference between the two study groups. Table 3 shows the metabolic parameters during exercise maximal of the HAPE-s and HAPE-r volunteers. Respiratory frequency and ventilation at the maximal exercise was significantly lower ($P<0.01$ and $P<0.05$, respectively) in HAPE-s participants than HAPE-r participants. Maximal oxygen consumption, maximal carbon dioxide output and maximal oxygen pulse was significantly lower ($P<0.01$, $P<0.001$ and $P<0.01$, respectively) in HAPE-s volunteers in comparison to HAPE-r volunteers. Maximal tidal volume and maximal heart rate are also lower in HAPE-s volunteers but the values were statistically not significant. Maximal ventilatory equivalent for oxygen and

Table 1. Anthropometric profile of the participants

Parameters	HAPE-s (n_1=7)	HAPE-r (n_2=7)
Age (years)	33.3 ± 4.5	31.9 ± 4.2
Height (cm)	170.9 ± 7.7	170.7 ± 4.2
Weight (kg)	68.8 ± 7.4	66.4 ± 6.6
BMI (kg.m^{-2})	24.8 ± 3.5	22.8 ± 2.6

Values are expressed as Mean ± SD. BMI: Body mass index.

Table 2. Resting metabolic profile of the participants

Parameters	HAPE-s (n_1=7)	HAPE-r (n_2=7)
f_{Rrest} (breaths.min^{-1})	16.6 ± 2.6	12.4 ± 2.9 *
$\dot{V}_{Trest}$ (L)	0.7 ± 0.4	0.6 ± 0.1
$\dot{V}_{Erest}$ (L.min^{-1})	9.2 ± 2.6	8.2 ± 1.0
$\dot{V}O_{2rest}$ (L.min^{-1})	0.27 ± 0.06	0.25 ± 0.06
$\dot{V}CO_{2rest}$ (L.min^{-1})	0.20 ± 0.04	0.20 ± 0.05
EqO_{2rest}	30.6 ± 3.4	29.9 ± 6.3
HR_{rest} (beats.min^{-1})	65.9 ± 7.2	59.4 ± 10.3
O_2P_{rest} (ml.beats^{-1})	3.8 ± 0.7	4.7 ± 0.8 *
RQ_{rest}	0.7 ± 0.1	0.8 ± 0.2

Values are expressed as Mean ± SD. * P <0.05., f_{Rrest}: Resting respiratory frequency, $\dot{V}_{Trest}$: Resting tidal volume, $\dot{V}_{Erest}$: Resting minute ventilation, $\dot{V}O_{2rest}$: Resting oxygen consumption, $\dot{V}CO_{2rest}$: Resting carbon dioxide output, EqO_{2rest}: Resting ventilatory equivalent for oxygen, HR_{rest}: Resting heart rate, O_2P_{rest}: Resting oxygen pulse and RQ_{rest}: Resting respiratory quotient.

Table 3. Metabolic response to exercise of the participants

Parameters	HAPE-s (n_1=7)	HAPE-r (n_2=7)
f_{Rmax} (breaths.min^{-1})	32.5 ± 4.5	50.6 ± 13.1 **
$\dot{V}_{Tmax}$ (L)	1.7 ± 0.4	2.1 ± 0.4
$\dot{V}_{Emax}$ (L.min^{-1})	59.7 ± 11.2	90.1 ± 26.7 *
$\dot{V}O_{2max}$ (L.min^{-1})	1.8 ± 0.4	2.8 ± 0.5 **
$\dot{V}CO_{2max}$ (L.min^{-1})	1.9 ± 0.4	2.7 ± 0.2 ***
EqO_{2max}	31.4 ± 7.1	31.6 ± 8.8
HR_{max} (beats.min^{-1})	170.0 ± 15.7	180.4 ± 11.6
O_2P_{max} (ml.beats^{-1})	11.7 ± 1.1	15.7 ± 3.2 **
RQ_{max}	1.0 ± 0.1	1.0 ± 0.2

Values are expressed as Mean ± SD. * P <0.05; ** P <0.01; *** P <0.001. f_{Rmax}: Maximal respiratory frequency, $\dot{V}_{Tmax}$: Maximal tidal volume, $\dot{V}_{Emax}$: Maximal minute ventilation, $\dot{V}O_{2max}$: Maximal oxygen consumption, $\dot{V}CO_{2max}$: Maximal carbon dioxide output, EqO_{2max}: Maximal ventilatory equivalent for oxygen, HR_{max}: Maximal heart rate, O_2P_{max}: Maximal oxygen pulse and RQ_{max}: Maximal respiratory quotient.

respiratory quotient at the time of maximal exercise also did not show any significant difference between the two study groups. Maximal work load was significantly lower (P<0.05) in HAPE-s volunteers than HAPE-r volunteers (Fig. 1). Pattern of oxygen consumption of HAPE-s and HAPE-r volunteers from resting to maximal exercise was shown in Fig. 2. Significant difference (P<0.01) was observed in oxygen consumption during maximal exercise between the two study groups.

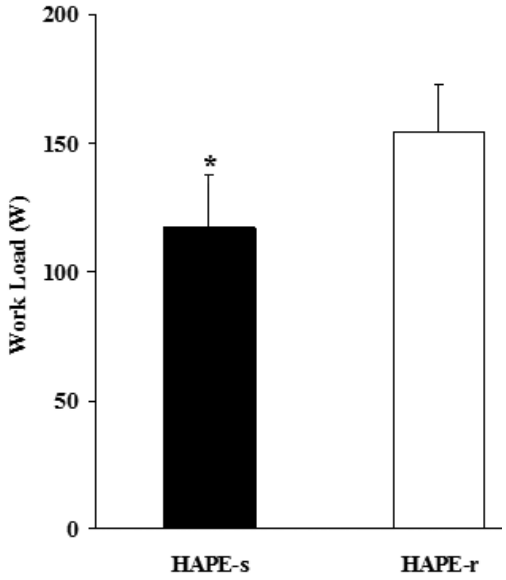

Figure 1. Maximal work load achieved during exercise.

Values are expressed as Mean ± SD. * P <0.05. HAPE-s: HAPE suitable volunteers, HAPE-r: HAPE resistant volunteers.

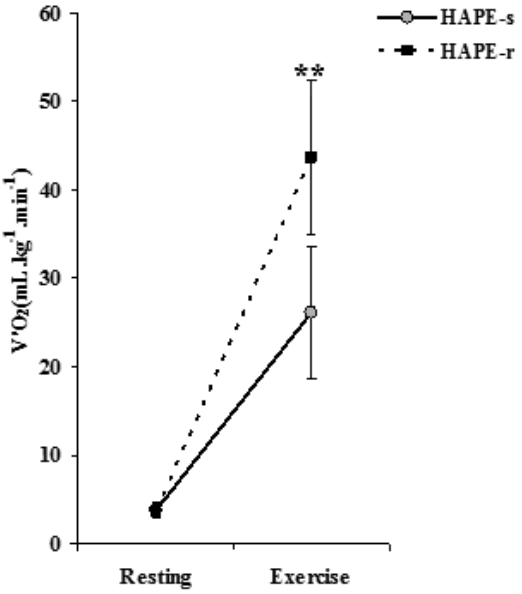

Figure 2. Pattern of oxygen consumption from resting to maximal exercise.

Values are expressed as Mean ± SD. ** P <0.01. HAPE-s: HAPE suitable volunteers, HAPE-r: HAPE resistant volunteers, $V'O_2$: Rate of oxygen consumption.

No significant difference was observed in resting oxygen consumption. Figures 3 and 4 shows the ventilatory responses from pre exercise to 100 W exercise of HAPE-s and HAPE-r volunteers. At pre-exercise and exercise at 0 W and 25 W load respiratory frequency of HAPE-s volunteers was significantly higher (P<0.05) than HAPE-r volunteers. Exercise at 0 W, 25 W, and 50 W load tidal volume of HAPE-s volunteers was significantly lower (P<0.05, P<0.05 and P<0.01, respectively) than HAPE-r volunteers. No significant difference was observed in ventilation between the two study groups. Rate of oxygen consumption of HAPE-s volunteers were significantly lower (P<0.05) than HAPE-r volunteers during exercise at 0

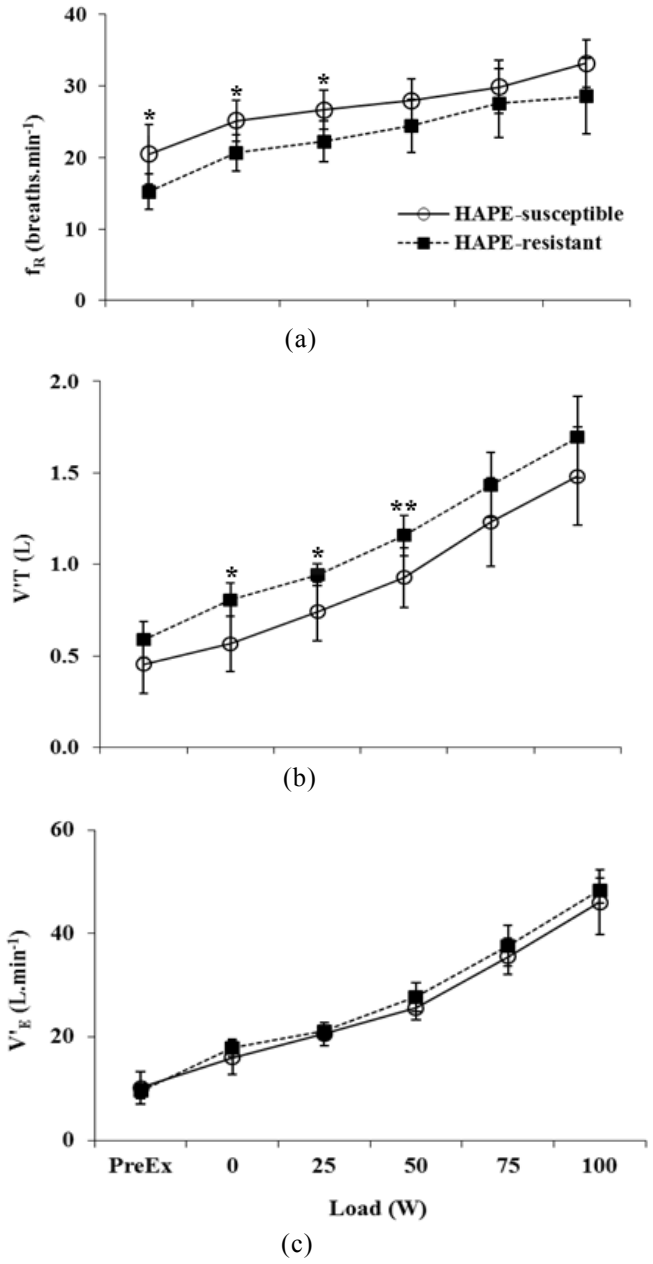

Figure 3. Respiratory frequency, tidal volume and ventilation response of HAPE-s and HAPE-r volunteers from pre-exercise to exercise up to 100 W load.

Values are expressed as Mean ± SD. * P <0.05; ** P <0.01. f_R: Respiratory frequency, V'$_T$: Tidal volume, V'$_E$: Minute ventilation.

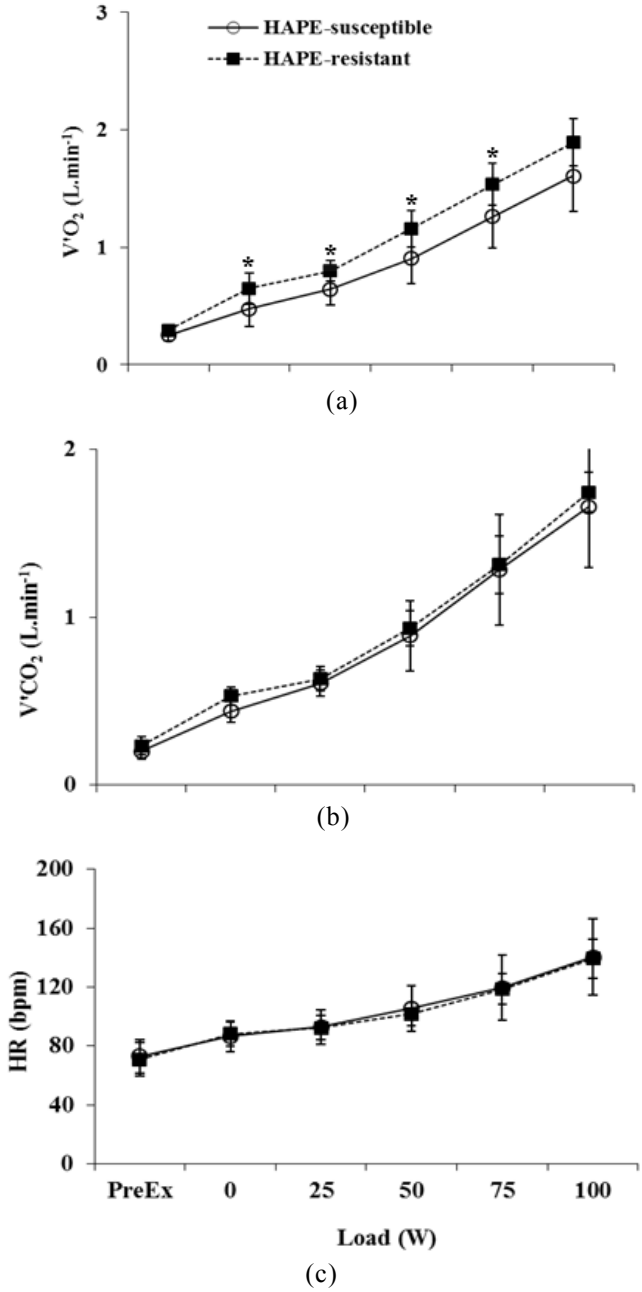

Figure 4. Rate of oxygen consumption, rate of carbon-di-oxide output and heart rate response of HAPE-s and HAPE-r volunteers from pre-exercise to exercise up to 100 W load.

Values are expressed as Mean ± SD. * P <0.05. V'O$_2$: Rate of oxygen consumption, V'CO$_2$: Rate of carbon dioxide output, HR: Heart rate.

W, 25 W, 50 W, and 75 W load. Rate of carbon dioxide output and heart rate did not show any significant changes between HAPE-s and HAPE-r volunteers.

4. DISCUSSIONS

The present study provides a detailed analysis of resting and exercise induced metabolic response of volunteers who had suffered from HAPE, in spite of pursuing proper acclimatization schedule, at a normobaric normoxic condition. The data was also compared with the volunteers who visited HA but did not suffer from the disease. The major findings of the study were that f_{Rrest} was higher in HAPE-s volunteers than HAPE-r volunteers. Whereas O_2P_{rest}, f_{Rmax}, $\dot{V}_{Emax}$, $\dot{V}O_{2max}$, $\dot{V}CO_{2max}$, O_2P_{max} and $Load_{max}$ of HAPE-s volunteers was lower in comparison to HAPE-r volunteers at sea level.

BMI of both the groups were under 'Normal' category according to WHO Expert Consultation Report[15]. Significantly higher resting respiratory frequency (25.3 %) of HAPE-s volunteers than HAPE-r volunteers might be due to increased sympathetic tone of the former[4]. This fact is also evident from a non significant but higher (9.9 %) resting heart rate of the former group. This is also in agreement with previous studies

from this Institute[16, 17] and others also[18]. As the vital capacity of the HAPE-s volunteers decreased due to alveolar fluid accumulation[19], heart and lungs of these volunteers have to work more to meet resting metabolic demand under similar condition.

During exercise f_R of HAPE-s volunteers was 25.8 per cent, 17.5 per cent and 16.8 per cent higher than HAPE-r volunteers at pre-exercise and exercise at 0 & 25 W load respectively. Respiratory frequency at the peak of exercise was 55.7 per cent lower in HAPE-s volunteers than HAPE-r volunteers. Ventilation of HAPE-s volunteers was lower than HAPE-r volunteers throughout the exercise. Maximal ventilation of HAPE-r volunteers was 50.9% higher than HAPE-s volunteers. The lower ventilation of HAPE-s volunteers might be due to lower lung volumes & capacities and reduced lung compliance, due accumulation of interstitial fluid and weakness of inspiratory muscles[20]. A lowered hypoxic pulmonary ventilatory responsiveness of HAPE-s volunteers during exercise also might be responsible for lower ventilation during exercise[21, 22]. Moreover, in a study with 8 HAPE-s and 5 control volunteers, it was reported that during exercise at normoxia, ventilation of HAPE-s group were lower than the control group at 30 per cent and at 50 per cent of $\dot{V}O_{2max}$[15]. It was also proposed that the lower ventilation of HAPE-s volunteers might be due to their 10 per cent smaller maximum lung volume than normal volunteers. The lower f_{Rmax}, $\dot{V}E_{max}$ and HR of HAPE-s volunteers, observed in the present study, also results a poor transport of O_2 to the locomotor muscles during maximal exercise, resulting a much lesser exercise capacity and physical endurance of those volunteers which is evident from the lower $Load_{max}$ (Fig. 1) during exercise maximal.

Maximal oxygen consumption and maximal carbon dioxide output of HAPE-s volunteers were 55.5 per cent and 42.1 per cent lower than HAPE-r volunteers. This lower $\dot{V}O_{2max}$ of HAPE-s volunteers might be due to their decreased cardiac output ($\dot{Q}$), stroke volume (SV) and lung diffusion capacity than HAPE-r volunteers during maximal exercise[13]. Thus the significant difference in $\dot{V}O_{2max}$ that we observed in acclimatised HAPE-s & HAPE-r volunteers might be due to differences in ventilatory haemodynamics of HAPE-s participants; more specifically exercise induced lower $\dot{V}E_{max}$, $\dot{Q}_{max}$ and lung diffusion capacity.

Kawashima[23], *et al.* measured pulmonary arterial pressure (PAP) in response to hypoxia, hypobaria and light exercise and observed a significant increase in PAP of HAPE-s volunteers in comparison to controls. In another study pulmonary vascular response (PAP and pulmonary arterial occlusion pressures) during heavy exercise was measured and reported that the pulmonary arterial pressure reactivity to exercise was significantly higher in the HAPE-s volunteers than control group[3]. In our study PAP of HAPE-s volunteers was higher than HAPE-r volunteers during resting condition at sea level (unpublished data). PAP of HAPE-s volunteers of the present study increased after proper acclimatization might be due to their heavy physical work during high altitude stay might also limit their maximal exercise capacity[24,25]. This pressure is further increased during exercise and results in augmented flow-dependent pulmonary vasoconstriction and/ or a reduction in pulmonary vascular cross-sectional area[13]. These incidents finally lower maximal aerobic capacity of HAPE-s participants than the control group.

Ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) mismatch is the imbalance between alveolar ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$). It has been established that during exercise this $\dot{V}_A/\dot{Q}$ mismatch is increased in both normoxia and hypoxia at sea level[26]. HAPE-s volunteers with higher alveolar vascular pressure would develop more exercise induced $\dot{V}_A/\dot{Q}$ mismatch than resistant volunteers due to excessive pulmonary $\dot{Q}$ in comparison to $\dot{V}_A$[27] and thus causes systemic arterial hypoxemia. In the present study we also observed that increased ventilation during exercise of HAPE-s volunteers was lower than the control group. It has been reported that the greater $\dot{V}_A/\dot{Q}$ inequality might be due to high pulmonary capillary pressure and/ or accumulation of temporary extravascular fluid inside the alveoli[28]. Reduction of pulmonary gas exchange of HAPE-s volunteers during resting and exercise might be due to more $\dot{V}_A/\dot{Q}$ mismatch and/or alveolar-end-capillary O_2 diffusion limitation[29]. In the present study during exercise, rate of oxygen consumption was lower in HAPE-s volunteers than HAPE-r volunteers from the beginning as shown in Fig. 4. Moreover due to a low hypoxic ventilatory response, there is an increase in hypoxemia in HAPE-s volunteers and thus results poor oxygen diffusion across the alveolar membrane during resting and exercise conditions.

One of the important parameter for the evaluation of cardio-vascular efficiency is O_2 pulse which is also closely related to health and cardiopulmonary function[30]. Resting O_2P was 23.7 per cent lower in HAPE-s volunteers than HAPE-r volunteers. A low O_2P_{max} of HAPE-s volunteers (34.2 % than HAPE-r volunteers) in the present study signifies a low stroke volume and cardiac output with an decreased oxygen delivery to the working muscles by each heart beat during exercise maximal, thus implicating a lower performance of the cardiovascular system of the HAPE-s volunteers. A lowered O_2P of HAPE-s volunteers also limits O_2 supply to the locomotor and ventilatory muscle that could lead to poor exercise performance at sea level as shown in Figs. 1 and 2.

It can be concluded from the present study that resting and exercise induced metabolic functions of HAPE-r volunteers was better as compared to HAPE-s volunteers at sea level.

CONFLICT OF INTEREST

None of the authors have any conflict of interest. All authors reviewed and approved the final draft of the manuscript.

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