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PULMONARY ARTERY PRESSURE IN LADAKHI MEN ON EXPOSURE TO ACUTE HYPOXIA AFTER A STAY AT SEA LEVEL

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Abstract : We had observed that very few Ladakhi soldiers (native highlanders : NHL) are hospitalized for high altitude pulmonary oedema. We hypothesized that this may happen because pulmonary artery pressures of NHLs do not increase even after exposure to acute hypoxia. The aim of this study was to test the above hypothesis by non-invasive echocardiographic assessment of pulmonary arterial pressure in freshly inducted Ladakhi soldiers and comparing it with that in freshly inducted lowlander soldiers (LL). The pre-ejection period and acceleration time ratio as measured from the pulmonary artery Doppler signal was used to compute mean pulmonary arterial pressure. In NHL this pressure on day 1 of induction was significantly lower at 25.8 ± 6.5 mmHg as compared to 31.9 ± 9.5 mmHg in LL (P = 0.0002). Another finding of interest was the very low Lake Louise acute mountain sickness score in the NHL (0.278 ± 0.461 on day 2). This appears to be further evidence that the natives of Ladakh are adapted to hypoxia and not merely acclimatized.

Key words : altitude adaptation echocardiography hypoxia vasoconstriction Ladakh

INTRODUCTION

Acclimatization occurs in sea-level residents exposed to hypobaric hypoxia of high altitude (HA). This phenomenon includes respiratory, cardiovascular, hematological and hormonal changes. In the long-term, changes in cellular oxidative enzyme systems are also believed to take place (1). One of the earliest response to HA is pulmonary hypoxic vasoconstriction (HVC) that may play a role in improving pulmonary ventilation-perfusion ratios. However unequal and exaggerated pulmonary HVC is a maladaptive phenomenon that has been implicated in the pathogenesis of high altitude pulmonary oedema (HAPO) (2). An increase in mean pulmonary arterial pressure ($P_{PulmArt}$) is the immediate expression of HVC.

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Men and women who do not acclimatize well are likely to suffer from one of the many high altitude maladies. The commonest amongst these are acute mountain sickness (AMS) and HAPO. The latter disease is the main cause of morbidity amongst the lowlander soldiers deployed at high altitude (3).

Our hospital records of the past 12 years showed that HAPO accounted for about 150–200 admissions per year. Of these, only 2–4 patients per year were natives of Ladakh (NHL). The remaining were all lowlanders. It is likely that this may be the result of a different response of the NHL to acute hypobaric hypoxia. Earlier studies at our Centre had shown evidence in favour of the Ladakhis being adapted to HA and not merely acclimatized (4, 5). We have hypothesized that Ladakhis have lower $P_{PulmArt}$ even when acutely exposed to high altitude (HA) as compared with $P_{PulmArt}$ of lowlander soldiers (LL) exposed to the same environment. This may contribute to the very low incidence of HAPO amongst NHL. We examined this hypothesis by measuring non-invasively $P_{PulmArt}$ of NHL and LL soldiers exposed to acute hypoxia of high altitude.

METHODS

The study was done at the High Altitude Medical Research Centre, Leh (altitude, 3450 m; mean atmospheric pressure, 505 mmHg).

The study group consisted of 40 volunteers from young healthy native highlander (NHL) males. These subjects had undergone a thorough medical examination prior to recruitment into the Army. This examination had been performed only 2 weeks before they volunteered as subjects for this study. They were being sent for military training in Aug 2000 to a town in the plains of Madhya Pradesh. For this study they were examined 2–4 days before leaving the HA area and were re-examined on returning to HA after a nine-month stay in the plains. We thus had a cohort of NHL whose high altitude stay was interrupted for a fairly long period of 9 months by a stay in the plains, before being re-inducted into their natural HA environment. Only 28 of the original 40 subjects were available for re-examination. Statistical analyses are therefore restricted to before and after data in 28 NHL subjects. The re-examination on re-entry to HA was conducted every day for 5 days immediately after arrival, starting 24 h after re-entry. The same parameters were studied before and after the training period in the plains. Informed consent was obtained from all subjects.

For the purpose of comparison the data from a group of 26 asymptomatic healthy male lowlander soldiers (LL), who had been posted to high altitude was used. These subjects were being examined concurrently as part of another study at our Centre. The LL underwent the same examinations as NHL except that they were not studied prior to leaving high altitude area and they were examined on the first 3 days and on Day 7 after entering HA.

In all subjects, resting heart rate (HR), respiratory rate (RR), and systemic arterial blood pressure were recorded using standard methods. Systemic arterial pressure was measured on days 1, 2, 4 and 5. Mean

systemic arterial pressure (MBP) was calculated as diastolic pressure +1/3 pulse pressure. Hemoglobin saturation (SaO_2) was measured with a pulse oximeter (Model 8500, Nonin, USA) using a finger probe. Blood samples were dawn for estimation of hemoglobin by the Drabkin's method.

The Lake Louise AMS scoring system was employed to diagnose AMS in both the groups. This widely accepted scoring system employs five symptoms and three signs each of which is graded according to its severity (6). A total score of 3 or more is considered to be diagnostic of AMS. The scoring was done on the first four days at HA.

Assessment of mean pulmonary artery pressure

This was done by echocardiography (SIM 2000, Esaote Biomedica, Italy) with a 3.5 MHz probe. The Doppler signal from the pulmonary artery just distal to the pulmonary valves was obtained in the left lateral position. The pre-ejection period (PEP; beginning of QRS complex to beginning of ejection), acceleration time (AT; beginning of ejection to the point of maximum velocity), and right ventricular ejection time (RVET; beginning of ejection to the end of ejection) were measured on the Doppler signals of the pulmonary artery flow. Each reading was taken in triplicate and the mean was calculated. The PEP/AT ratio was used to compute $P_{PulmArt}$ using the regression equation proposed by Vijan et al viz. mean $P_{PulmArt}$ = (23.94*(PEP/AT))+2.44 (7).

Tricuspid valve mean E/A ratio were calculated from three cardiac cycles. In echocardiography, the early diastolic flow of blood through the atrio-ventricular valves produces a Doppler signal that is termed the E wave while the flow that occurs during atrial contraction is termed the A wave.

Statistical analysis

One-way within-subjects repeated measures ANOVA design was used to look for significantly different values within each group (alpha = 0.05). The data from NHL and from LL was analyzed separately. Comparisons for a particular day at HA between the 2 samples were done using the unpaired t-test assuming unequal variance. All values are reported as mean ± standard deviation.

RESULTS

The mean age of the NHL subjects (n = 40) in August 2000 was 20.2 ± 0.62 years. The mean height was 164.8 ± 5.54 cm and mean weight was 59.5 ± 6.5 kg. On reinduction to HA, in April 2001, the mean height and mean weight, of the 28 subjects who returned, were 165.2 ± 4.1 cm and 61.7 ± 5.3 kg respectively. The mean age of the LL group was 32.7 ± 6.9 years, mean height 167.7 ± 7.32 cm and mean weight 64.09 ± 5.55 kg.

Heart rate and blood pressure (Table I)

The baseline HR in the study group was 64.6 ± 7.4 beats/min. On day 1, after returning to HA the HR was 67.5 ± 11.4 beats/min and thereafter increased to a

TABLE I : Heart rate, blood pressure, and oxygen saturation in Ladakhi and lowlander soldiers at high altitude (HA).

	Baseline (HA)	*Day 1 at HA*	*Day 2 at HA*	*Day 3 at HA*	*Day 4 at HA*	*Day 5 at HA (Day 7 for LL)*
Heart rate (bpm)						
Ladakhi	65.6±7.4	67.5±11.4*	63.1±10.6*	74.0±11.0	72.8±8.6	70.1±8.6
Lowlanders	–	77.4±11.6	75.6±10.2	75.5±12.1	–	75.5±14.7
Systolic blood pressure (mmHg)						
Ladakhi	117.5±8.7	119.2±13.9	117.7±9.2	–	115.0±12.9	115.5±12.1
Lowlanders	–	128.1±9.9	126.8±8.6	125.2±11.1	–	–
Diastolic blood pressure (mmHg)						
Ladakhi	63.1±6.7	71.6±9.5	71.8±6.3	–	72.5±5.0	71.0±7.3
Lowlanders	–	73.7±11.6	73.0±7.3	72.6±7.7	–	–
SaO_2 (%)						
Ladakhi	86.4±2.9	88.0±2.6	88.9±1.3	90.4±1.5*	90.1±1.6	90.0±1.7
Lowlanders	–	88.3±2.8	88.9±2.5	88.9±2.4	–	90.1±1.9

(*denotes NHL value significantly different from LL for the same day)

significant maximum on day 3 (P<0.0001). HR in the control group (LL) was the highest on day 1 and fell only slightly by day 7 (P = 0.8330). The HR in the NHL was significantly lower than in the LL on days 1 and 2 (P = 0.0199 and P = 0.0137 respectively).

Mean systemic blood pressure reflected the changes in HR. In the NHL baseline MBP was the lowest at 81.2 ± 7.1 mmHg, and reached a maximum on day 2 (87.2 ± 6.8 mmHg, P = 0.0041). The MBP in the LL was the highest on day 1 (91.84 ± 8.03 mmHg) but fell slightly on days 2 and 3 and very little thereafter (P = 0.3617).

SaO_2 (Table I) and respiratory rate

Baseline SaO_2 in the NHL was only 86.4%. On day 1 at HA it was 88.0 ± 2.6% and increased to 90.4 ± 1.5% (P<0.0001) by day 3. This latter value was significantly higher (P = 0.007) than the day 3 value in the LL where it was 88.9 ± 2.4%. There was little change after that. In the LL the SaO_2 increased very gradually over the seven days being 88.3 ± 2.8% on day 1 and 90.1 ± 1.9% on day 7 (P = 0.0166).

There was no significant difference in the resting respiratory rate in either of the groups on day 1 or later.

Estimated mean pulmonary arterial pressure (Table II)

The baseline $P_{PulmArt}$ in NHL was 24.8 ± 4.1 mmHg. On day 1 it was marginally higher at 25.7 ± 6.5 mmHg and then marginally lower on days 3–5 (lowest on day 3, 23.6 ± 4.0 mmHg, P = 0.3584). In the LL $P_{PulmArt}$ was 31.9 ± 9.5 mmHg on day 1 and then increased marginally to a maximum of 32.7 ± 6.1 mmHg on day 3 (P = 0.6523). However $P_{PulmArt}$ in the NHL was significantly lower at all times in comparison with LL (Fig 1; P = 0.00019, P =0.000014, and P<0.00001 on days 1, 2 and 3 respectively).

TABLE II : Mean pulmonary arterial pressure and tricuspid valve E/A ratios in Ladakhi and lowlander soldiers at high altitude (HA).

	Baseline (HA)	*Day 1 at HA*	*Day 2 at HA*	*Day 3 at HA*	*Day 4 at HA*	*Day 5 at HA (Day 7 for LL)*
Mean pulmonary arterial pressure (mmHg)						
Ladakhi	24.8±4.1	25.7±6.5*	25.8±3.7*	23.6±4.0*	24.0±4.6	23.8±3.2
Lowlanders	–	31.9±9.5	32.3±8.4	32.7±6.1	–	30.7±6.9
Tricuspid valve E/A ratio						
Ladakhi	2.51±0.89	2.74±0.81*	2.25±0.69*	2.16±0.82*	2.16±0.79	2.02±0.69
Lowlanders	–	1.28±0.34	1.40±0.39	1.41±0.36	–	1.58±0.56

(*denotes NHL value significantly different from LL for the same day)

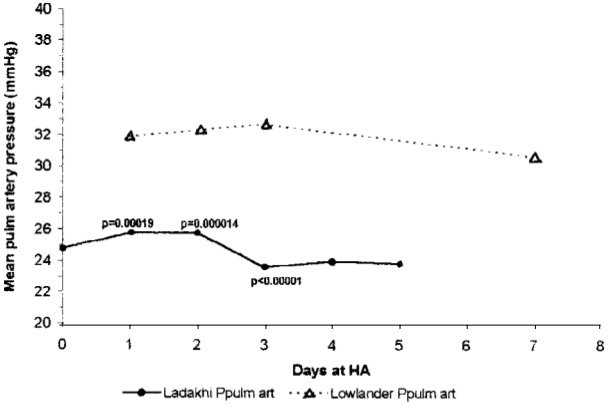

Fig. 1 : Mean pulmonary artery ($P_{PulmArt}$) pressure in Ladakhi natives and lowlanders during first week at 3450 metres.

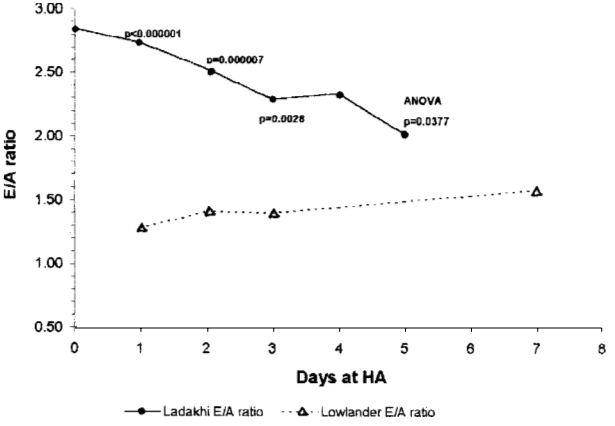

Fig. 2 : Tricuspid valve E/A ratio in Ladakhi natives and lowlanders first week at 3450 metres.

Tricuspid valve E/A ratios (Table II)

Tricuspid valve E/A ratio on day 1 was 2.74 ± 0.81 in NHL and showed a significant downward trend till day 5 (2.02 ± 0.69, P = 0.0377). In the LL, on the other hand there was only a slight increase between day 1 and day 7 values (1.28 ± 0.34 vs 1.58 ± 0.56, P = 0.374). The NHL had highly significantly greater E/A ratio than LL on all days (Fig. 2; P<0.000001, P = 0.000007, and P = 0.0028 on days 1, 2 and 3 respectively).

Lake Louise AMS scores

In the NHL group the maximum mean Lake Louise AMS score was on day 2 and was only 0.278 ± 0.461. The scores on other days did not vary significantly (P = 0.1597). None of the NHL subjects scored more than 1 on any day during the study hence none was diagnosed as AMS. On the other hand in the LL group though the mean Lake Louise score on day 1 was only 0.810 ± 1.167 yet there were three men who scored 3 and qualified to be diagnosed as AMS. The day

1 mean score in LL was significantly higher than in the NHL (P = 0.0012). By the second day all the three subjects with AMS scored 2 or less but a fourth subject scored 3. On day 2 the differences were not significant (P = 0.063). By day 3 the mean Lake Louise score in the LL was 0.0190 ± 0.402 and none of the subjects had a score more than 1. None of the subjects in the two groups developed HAPO.

Hemoglobin concentration

The hemoglobin concentration in NHL subjects before they left for the plains was 14.88 ± 0.77 g/dL. This remained unchanged on return and was 15.07 ± 0.87 g/dL when measured on day 1 at high altitude (P = 0.393). The hemoglobin concentration in the LL was 15.43 ± 0.65 g/dL statistically similar to that in NHL.

DISCUSSION

The salient finding of this study was that echocardiographically determined $P_{PulmArt}$ was significant lower in the NHL during the first 5 days at HA compared to that LL. On the first 3 days the difference was highly significant (Table II). Additionally, the $P_{PulmArt}$ in NHL did not show the increase during the first three days as seen in the LL. On the contrary the day 3 $P_{PulmArt}$ in the NHL was the lowest (23.6 ± 4.0 mmHg) during the 5 days that they were examined, whereas in the LL $P_{PulmArt}$ was at its highest on day 3. We did not measure $P_{PulmArt}$ on the 4th to the 6th day in the LL hence no comments are offered on the changes in $P_{PulmArt}$ in this group during that period. However the day 7 values were the lowest in the LL and it is likely that $P_{PulmArt}$ would have started dropping after day 3.

The range of estimated $P_{PulmArt}$ in NHL and LL in this study was 23.6 to 25.8 mmHg and 30.7 to 32.7 mmHg respectively. These mean pressures are high compared to what is expected in normal individuals at HA. In an earlier study, in which pulmonary artery pressures were measured invasively by catheterization, we found the $P_{PulmArt}$ in NHL to be 14 mmHg (5). The subjects of this study were also natives of Ladakh but had been at HA continuously for over a year. Groves et al recorded similar $P_{PulmArt}$ (15 mmHg) at rest in 5 Tibetan subjects (8). These values are much lower compared to the echocardiographically computed baseline $P_{PulmArt}$ in our present group of NHL subjects (24.8 ± 4.1 mmHg). Thus echocardiographically computed $P_{PulmArt}$ appears to have overestimated actual $P_{PulmArt}$. However in the present study we were looking at the changes in this pressure during exposure to acute hypoxia and not the absolute values. Further, since we were interested in the $P_{PulmArt}$ serially over several days in the same subjects an invasive procedure was not practical and could not have been used. To our knowledge, this is the first ever study where the serial $P_{PulmArt}$ response across 5 days in the native Ladakhi on re-induction to HA has been studied non-invasively.

Several authors have proposed regression equations to estimate mean pulmonary artery pressures from echocardiographic systolic time intervals (7, 9, 10). We chose the regression proposed by Vijan et al [$P_{PulmArt}$ = (23.94* (PEP/AT)+2.44] as this was based on a study on Indian subjects. Other regression equations would have given us different absolute values for the $P_{PulmArt}$ but the relative difference between NHL and LL and the trend of day-to-day change would have remained unchanged.

In our experience most patients with HAPO develop symptoms 48–96 h after arrival at HA with a peak at about 72 h. Our finding, of gradually increasing $P_{PulmArt}$ in the LL group till 72 h, though not statistically significant, is in consonance with this clinical fact. It is known that patients who have suffered from HAPO show an exaggerated HVC (11). None of our subjects suffered from HAPO hence we did not find any significant rise in $P_{PulmArt}$ in LL ($P = 0.6523$).

Doppler interrogation of blood flow through the tricuspid valve yields a biphasic flow signal. The early peak (E wave) coincides with early diastolic filling and the second peak with atrial systole (A wave). Normally the E wave is of a higher velocity. It has been shown that factors like raised end-diastolic right ventricular pressure, increased pulmonary artery pressure, and reduced compliance of the ventricle can impede the free flow of blood during the early passive filling phase. This results in the reduction of peak velocity of the E wave till it is equal to, or even less than, the A wave peak velocity. This has been clearly brought out in our study. The E/A ratio was significantly higher in NHL than LL. This reflected the relative resistance to early filling of the right ventricle in the LL. Hence in this group E/A ratios were closer to 1 in contrast to the NHL (Table II).

There is tachycardia on exposure to HA. This is due to the generalized increase in sympatho-adrenal activity that occurs at HA especially during the first 10 days. This effect is later blunted (12). This would explain the small reduction in HR and MBP seen after the first day at HA in the LL (Table I). The HR response in the NHL did not show this pattern. The HR was only 67.5 ± 11.4 on day 1 and increased significantly to 74.0 ± 11.0 on day 3. At this point of time it is not possible to comment on the reasons for this finding. The baseline HR in the NHL was lower than is normally found in healthy lowlander individuals in the plains.

Hemoglobin saturation was virtually the same in the two groups during the study period. Hence oxygen carrying capacity of the blood in both groups was similar.

Another finding of particular interest in this study was the very low Lake Louise score reported in the NHL. As indicated by the low Lake Louis scores, none of the NHLs developed AMS. Also their $P_{PulmArt}$ was low. Those who suffer from AMS have a Lake Louis score of at least 3 as well as a high $P_{PulmArt}$ (as seen in 4 of the LL). There are greater chances of such subjects developing HAPO. These findings may partly explain why there is a negligible incidence of HAPO in the NHL. Earlier studies at HAMRC have shown that Ladakhi men have thinner muscular layers in the small pulmonary arterioles as compared to the South American Indians who are also ordinarily resident at high altitude (4). This may result in a weaker hypoxic vasoconstrictive response to acute hypoxia and thus lower pulmonary arterial pressures.

We recognize that the two groups were not age-matched and it may be argued that this may have influenced our results. The subjects in the LL group were significantly older than the NHL. However clinical experience at this Centre and various earlier studies have not shown any age-related differences in $P_{PulmArt}$. On the contrary the young appear to suffer more often from

HAPO and hence ought to be the group with higher $P_{PulmArt}$. In our earlier study (5) the mean age of the NHL group was 28 years yet their $P_{PulmArt}$ was much lower than in the LL. It is therefore suggested that no important interaction exists between age and the hypoxic vasoconstrictive response at HA and that the age difference amongst groups in the present study would not have vitiated our results. It is also true that the NHL group was drawn from amongst young recruits and it was not possible to draw the LL sample from recruits since LL recruits are never brought to HA for training.

In conclusion we report that the pulmonary artery pressure in the Ladakhis was consistently and significantly lower than in the lowlanders during acute hypoxic exposure. The oxygen carrying capacity was similar in both groups. Yet the Ladakhis achieved significantly better hemoglobin saturation by day 3 and also had significantly low Lake Louise AMS scores. These results help to explain the low incidence of HAPO amongst the Ladakhis in comparison to lowlanders.

The Ladakhi population has been resident at high altitude for a period long enough to accumulate genetic changes that are of advantage in a hypoxic environment. This may have resulted in an inherited adaptation to HA. The present study provides indirect evidence that the Ladakhi native is adapted to his environment and not merely acclimatized and that this adaptation extends to the hemodynamic response of the pulmonary circulation to hypobaric hypoxia.

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