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Original Article

Ventilatory parameters at rest after months of stay at 3300 m: A comparison between acclimatized lowlanders and natives at Leh

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ABSTRACT

Background: Increased pulmonary ventilation helps lowlanders and natives to maintain arterial oxygenation at high altitudes. Natives of Ladakh have been shown to have similar ventilatory parameters as Tibetans at 3300 m. But there is limited literature comparing these parameters in Ladakhi natives with acclimatized lowland sojourners.

Methods: End-tidal carbon dioxide partial pressure (EtCO₂), blood oxygen saturation (SpO₂) and hemoglobin concentration (Hb) were measured in 276 participants, 126 native highlanders (NHL – 40 females, 86 males) and 150 acclimatized lowlanders (ALL – 60 females, 90 males).

Results: EtCO₂ was greater in the NHL compared to the ALL, (33.8 ± 3.3 vs 31 ± 2.5 mmHg) although SpO₂ was lower (90.9 ± 2.4 vs 91.7 ± 2.3%). When grouped by sex, NHL males had significantly greater EtCO₂ than NHL females, ALL males and ALL females. Hb and calculated arterial oxygen content was similar in Ladakhis and acclimatized lowlanders, although greater in males compared to females. Systemic blood pressure, heart rate and the proportion of hypertensives was significantly greater in the ALL.

Conclusion: Native Ladakhis, have a significantly greater resting EtCO₂ (especially in males) and lower SpO₂ than acclimatized lowlanders. Blood Hb concentration and oxygen content is, however, similar in natives and acclimatized lowlanders of the same sex.

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Introduction

Ventilation at rest is regulated, in the short and long term, by multiple factors that may be broadly grouped as chemical and neural factors. Chemical factors regulating ventilation include arterial oxygen tension (PaO_2), arterial carbon dioxide tension (PaCO_2) and pH, while neural factors comprise inputs from brainstem respiratory neurons, cortical inputs and various vagally-mediated reflexes.¹ Neurotransmitters and hormones such as catecholamines, progesterone, estrogen, serotonin, substance P and nitric oxide may modulate ventilation over longer time frames.²

The CO_2 level in blood, hence PaCO_2 , is a balance of gas produced metabolically versus that removed by ventilation. In health, at rest, in normoxemic adult men, blood carbon dioxide regulates ventilation, such that PaCO_2 remains constant at values between 36 and 42 mmHg.³ This is achieved by the action of CO_2 on central and peripheral chemoreceptors. However, in hypobaric hypoxia, as found at high altitudes, oxygen by its action on the carotid body chemoreceptors, is the principal regulator of ventilation. The hypoxic ventilatory response (HVR) to high altitude exposure, in healthy acclimatizing lowland sojourners, increases over the first few days to weeks at high altitude (HA), by increasing sensitivity of the carotid chemoreceptors. The increased ventilation is, thereafter, sustained for the duration of stay at HA.² In natives adapted by generations of stay at HA, the HVR appears to have been affected differently in different ethnic groups, the Tibetan highlander having retained the HVR and the Andean highlander having a reduced response. It has been shown that the Tibetan highlander has similar resting ventilation at HA as acclimatized lowlanders and manifests increased ventilation on further ascent. Andeans on the other hand, have relatively lower ventilatory response and adapt, instead, by an increase in hemoglobin that is not seen in Tibetans.⁴

Ladakh is a remote trans-Himalayan region of India with its district administrative headquarters at Leh, at an altitude of 3300 m. The people of Ladakh are believed to be of mixed Tibetan and Dard ethnicity.⁵ A large population of natives lives here between altitudes of 2500–4500 m and many facets of the adaptations to HA in this unique ethnic group have been studied. We could, however, not find any head to head comparison of cardiorespiratory variables in native Ladakhis and lowland sojourners staying at the same altitude for periods of months to years.

Studies of cardiorespiratory variables in Ladakhi women are also few.⁶ Near sea-level, women show higher ventilation and lower EtCO_2 than men at rest, due to effects of gonadal steroids.^{7,8} Hormonal involvement in ventilatory control is, also, evident in the cyclic fluctuation in ventilation during the menstrual cycle.^{8,9} Some studies report that women have higher resting ventilation, in the first week after ascent to HA, that may confer protection against acute altitude illness, while others, done after short hypoxic exposures, report a similar increase in ventilation, regardless of sex, on exposure to hypoxia.^{8,10,11} However, most studies to date have reported findings of ventilatory changes over only few hours to days of hypoxic exposure.^{10,12,13}

PaCO_2 correlates well with partial pressure of carbon dioxide in end-tidal air (EtCO_2), across all dead space volumes, in healthy subjects with normal ventilation-perfusion ratio and dead space volume. Measurement of EtCO_2 is therefore, used as a reliable, non-invasive marker of carbon dioxide partial pressure in the blood.¹⁴ In turn, in healthy people at rest, EtCO_2 may serve as a reliable marker of ventilation, increasing with lower ventilation and vice versa.

This study, therefore aimed to compare cardio-respiratory parameters, including EtCO_2 , SpO_2 , heart rate (HR), Hb and CaO_2 at rest in native highland men and women of Ladakh, resident at an altitude of 3300 m, with acclimatized lowland sojourners staying at the same altitude for weeks to months. It was expected that pre-menopausal females at high altitude, whether acclimatized lowlanders or native highlanders, would have greater resting ventilation than their male counterparts.

Material and methods

Selection of subjects

A total of 380 subjects, consisting of 192 native highland Ladakhis (NHL) and 188 acclimatized lowlanders (ALL), provided written informed consent, and were enlisted for this cross-sectional study from September to December 2010. Approval for conduct of the study was obtained from the institutional review board and ethics committee. Native highlanders were recruited through broadcast in the community hall of the village Pheyang, Leh. The ALL group consisted of men and women, born and belonging to near sea-level areas in northern and central parts of India, sojourning at 3300 m. Inclusion criteria for the study were (a) healthy adult males and females, aged between 18 and 50 years and (b) ALL subjects with uneventful stay at high altitude, of at least one month. Exclusion criteria were (a) change in altitude within one month preceding the study, (b) concurrent respiratory or cardiovascular illness, (c) anemia, (d) trained athletes and for only female participants (e) presence of menstrual irregularities (f) on hormonal contraceptives and (g) post-menopausal status. Sixty-nine participants did not meet the study criteria, while thirty-five subjects refused withdrawal of blood sample for determination of Hb (Fig. 1).

Study design

The study was conducted at a high altitude lab in Leh, Ladakh, at an altitude of 3300 m and ambient barometric pressure 510 mmHg. The participants were instructed to report in the morning on the day of test, after a light breakfast and advised avoidance of physical exertion, smoking, intake of coffee and tea on the day of the test. Those who had consumed alcohol in the 24 h preceding testing were advised to return after 24 h abstinence. Detailed history was obtained and clinical examination performed to rule out any chronic illness/disease, especially respiratory disorders. Menstrual history was obtained in women.

Fig. 1 – Recruitment of subjects in various groups: The flow chart illustrates the number of subjects recruited for the study at Pheyang and Leh, alongwith reasons for non-participation at each stage. NHLM: native highland males; NHLF: native highland females; ALLM: acclimatized lowland males; ALLF: acclimatized lowland females.

The parameters recorded in the study included EtCO₂, SpO₂, heart rate (HR), systemic blood pressure (BP), respiratory rate (RR) and hemoglobin concentration (Hb). A multiparameter monitor (Model MPM 5553 Pro, BPL limited, India) was used to record EtCO₂ and SpO₂ as per standard guidelines.¹⁵ EtCO₂ was measured by sidestream capnography, which was calibrated with room air before each measurement. Pulse oximetry by the multiparameter monitor had been validated against hemoglobin-oxygen saturation measured by co-oximetry on arterial blood samples. Blood pressure was recorded using a digital BP monitor (Omron T8 Blood Pressure monitor model T8 HEM-757A-C1) as per JNC VII guidelines.¹⁶ All measurements were made in seated subjects, after 15 min of rest in the clinic, with ambient temperatures between 22 °C and 26 °C. Respiratory rate was measured before wearing the face mask and allowed to settle with the mask, to the earlier value before recording EtCO₂. Schloesing Automated Hematology Analyzer (MS-4C, Melet Schloesing Laboratories, France) was used for estimation of hemoglobin. Arterial oxygen content (CaO₂) was calculated using the formula¹⁷ $CaO_2 = SpO_2 \cdot Hb \cdot 1.34 / 100$.

Statistical analysis

The data was analyzed using IBM SPSS statistical software version 20 (IBM Corp Armonk NY, 2011). Descriptive statistics like mean, standard deviation (SD) and range are reported, where applicable. Test of homogeneity was applied to compare the variations between study groups. One-way analysis of variance (ANOVA) was performed to analyze differences of means between groups, followed by post hoc Bonferroni test for multiple comparisons. The results were taken as significant when *p* was less than 0.05.

Results

Demographic characteristics of the subjects, are shown in Table 1. The NHL and ALL were of similar age, but the ALL, especially ALLF had significantly greater BMI. The NHL group had a greater EtCO₂, similar RR and Hb, but lesser SpO₂, HR, and systemic BP compared to the ALL (Table 2). The subjects were also divided by sex into NHL female (NHLF), NHL male (NHLM), ALL female (ALLF) and ALL male (ALLM) for analysis (Table 3). The effect of smoking on cardio-respiratory parameters was studied, by dividing NHLM and ALLM into smokers (NHLMS/ALLMS) and non-smokers (NHLMSns/ALLMSns). Because the females did not have significant numbers of smokers, one and five females in the ALLF and NHLF respectively being smokers, these groups were not subdivided by smoking status. The prevalence of smokers among the NHLM and ALLM, 27% versus 21% respectively, was not different (95% CI – 7.4% to 19.2%, Chi-square = 0.571, *p* = 0.4497) (Appendix A – Supplementary Table).

The mean BMI of the ALLF was significantly greater than that of all other groups except smokers of either group. However, subjects of all groups had mean BMI values within the normal range. Among the ALL, mean age and duration of stay at HA was not significantly different between the sexes.

The NHLM had significantly higher mean EtCO₂ compared to all other groups. Smokers of either group, NHLM and ALLM, had higher EtCO₂ values than non-smokers. EtCO₂ values in NHLM (smokers and non-smokers) were significantly higher than the other four groups all of which had insignificantly different mean EtCO₂. Respiratory rate was insignificantly different between groups (Appendix A – Supplementary Table).

SpO₂ was significantly greater in ALLF than in all other groups which had insignificantly different SpO₂ values.

Table 1 – Demographic profile of study population: All the values are expressed as mean $\pm$ SD (range). One-way ANOVA and post hoc test (Bonferroni) is used to calculate difference of means between the four groups.

Study population	Number of individuals in the group	Age (years)	Duration of stay at 3300 m (days)	BMI (kg/m ²)
		Mean $\pm$ SD (range)	Mean $\pm$ SD (range)	Mean $\pm$ SD (range)
ALL	150	30.9 $\pm$ 6.7 (20–49)	252 $\pm$ 204 (30–1230)	23.1 $\pm$ 2.3 ^{a,*} (18.3–30.3)
NHL	126	29.6 $\pm$ 7.7 (18–48)	Life long	22.2 $\pm$ 2.2 (16.7–28.5)
ALLM	90	30 $\pm$ 7 (20–45)	246 $\pm$ 158 (30–730)	22.7 $\pm$ 1.7 (19–27)
NHLM	86	29 $\pm$ 6 (18–46)	Life-long	22.2 $\pm$ 2 (17–27)
ALLF	60	31 $\pm$ 6 (23–44)	295 $\pm$ 330 (30–1230)	24 $\pm$ 3 ^{b,*} (20–30)
NHLF	40	31 $\pm$ 6 (19–45)	Life-long	22.2 $\pm$ 3 (20–29)

ALLM: acclimatized lowland males; NHLM: native highland males; ALLF: acclimatized lowland females; NHLF: native highland females; BMI: body mass index.
^{*} $p < 0.05$ is taken as significant difference.
^a ALL > NHL.
^b ALLF > other sex-based groups.

Table 2 – Cardio-respiratory parameters in native highlanders and acclimatized lowlanders. This table shows difference in various cardio-respiratory parameters between acclimatized lowlanders and native highlanders, analyzed using Student's t-test. All values are represented as mean $\pm$ SD (95% confidence interval) and range.

Parameter (units)	ALL (n = 150)	NHL (n = 126)	'p' value
EtCO ₂ (mm Hg)	31 $\pm$ 2.5 (30.6–31.4) 24–38	33.8 $\pm$ 3.3 (33.3–34.4) 26–43	<0.0001 [*]
SpO ₂ (%)	91.7 $\pm$ 2.3 (91.6–92.3) 86–98	90.9 $\pm$ 2.4 (90.5–91.3) 85–96	0.0001 [*]
Hb (g/dL)	15.4 $\pm$ 1.9 (15.1–15.8) 12–19.3	15.5 $\pm$ 1.6 (15.2–15.8) 11.3–18.8	0.67
CaO ₂ (mLO ₂ /dL blood)	19.02 $\pm$ 2.3 (18.6–19.4) 14.5–24	18.9 $\pm$ 2 (18.5–19.3) 14–23.4	0.7
Heart rate (beats per minute)	83.7 $\pm$ 11.6 (81.8–85.6) 57–120	73.4 $\pm$ 10.2 (71.6–75) 50–102	<0.0001 [*]
Respiratory rate (per minute)	18.5 $\pm$ 3 (18–19) 12–25	19.7 $\pm$ 3.2 (19–20.2) 12–27	0.003 [*]
SBP (mmHg)	126 $\pm$ 10.7 (124.4–127.8) 100–146	123 $\pm$ 10.5 (121–125) 100–146	0.01 [*]
DBP (mmHg)	82.6 $\pm$ 7.4 (81.5–83.8) 64–96	76.3 $\pm$ 8.7 (74.7–77.8) 54–98	<0.0001 [*]

ALL: acclimatized lowlanders; NHL: native highlanders; EtCO₂: end-tidal carbon dioxide; SpO₂: oxygen saturation; Hb: hemoglobin; CaO₂: arterial oxygen content; SBP: systolic blood pressure; DBP: diastolic blood pressure.
^{*} $p < 0.05$ is taken as significant.

Hemoglobin and calculated arterial oxygen content was similar in NHLM and ALLM regardless of smoking status but significantly greater than in women, native or sojourners. Acclimatized sojourners, also, had higher blood pressure and heart rate than the native men and women (Table 2). The prevalence of hypertension (BP $\geq$ 140/90 mmHg) was significantly greater in ALL than in NHL (31.33% versus 13.49%) and in

ALLM (34/90 = 37.78%) than in NHLM (8/86 = 9.3%), ALLF (13/60 = 21.67%) and NHLF (9/40 = 22.5%).

Other than the native highland women, who had a significant positive correlation of age with Hb ($r = 0.37$, $p = 0.03$) none of the other groups had significant correlation of age/duration of stay with Hb ($r = -0.14$ to 0.18 , $p = 0.13$ – 0.22).

Table 3 – Cardio-respiratory parameters in males and females of native highlander and acclimatized lowlander groups. This table shows difference in cardio-respiratory parameters between the acclimatized lowlanders and native highlanders, when divided into four sub-groups, ALLM, NHLM, ALLF, NHLF, analyzed using one-way ANOVA. All values are represented as mean $\pm$ SD (95% confidence interval) and range.

Parameter	ALLM (n = 90)	NHLM (n = 86)	ALLF (n = 60)	NHLF (n = 40)	'p' value for 1-way ANOVA	Post hoc Bonferroni's test*
EtCO ₂ (mm Hg)	31 $\pm$ 3 (30–32) 20–45	35 $\pm$ 3* (34–36) 18–46	31 $\pm$ 2 (29–31) 23–44	32 $\pm$ 3 (29–33) 19–40	<0.0001	NHLM > All other groups. Other groups similar.
SpO ₂ (%)	91 $\pm$ 2 (91–92) 86–97	91 $\pm$ 2 (90–91) 85–96	93 $\pm$ 2* (92–94) 89–98	91 $\pm$ 2 (90–93) 88–94	<0.0001	ALLF > All other groups. Other groups similar.
Hb (g/dL)	16.7 $\pm$ 1.3* (16.4–17.0) 13.9–19.3	16.3 $\pm$ 1.1* (16–16.5) 13.5–18.8	13.7 $\pm$ 0.8 (13.4–14.0) 12.4–15.3	13.7 $\pm$ 0.9 (12.8–14.1) 11.3–14.6	<0.0001	ALLM = NHLM > Female groups. Female groups similar.
CaO ₂ (mLO ₂ /dL blood)	20.4 $\pm$ 1.8* (20–20.8) 16.0–24.0	19.8 $\pm$ 1.5* (19.5–20.2) 16.5–23.4	17.0 $\pm$ 1.1 (16.7–17.6) 15.1–19.7	16.7 $\pm$ 1.0 (15.8–17.2) 15.2–18.2	<0.0001	ALLM = NHLM > Female groups. Female groups similar.
Heart rate (Bpm)	80.5 $\pm$ 10.5 (78.3–82.7) 57–110	71.2 $\pm$ 10.2* (69–73.4) 50–94	88.5 $\pm$ 11.5* (85.5–91.5) 66–120	78 $\pm$ 8.6 (75–80.7) 62–102	<0.0001	ALLF > ALLM = NHLF NHLM < All other groups.
Respiratory rate (per minute)	18.4 $\pm$ 3.2 (17.7–19) 12–25	19.8 $\pm$ 3.3* (19.1–20.5) 12–27	18.7 $\pm$ 2.5 (18.1–19.4) 13–25	19.3 $\pm$ 3 (18.3–20.3) 15–27	0.02	NHLM > ALLM
SBP (mmHg)	129.8 $\pm$ 9* (128–131.7) 105–146	122.7 $\pm$ 10.1 (120.6–125) 104–140	120.4 $\pm$ 10.5 (117.7–123) 100–142	123.8 $\pm$ 11.4 (120–127.4) 100–146	<0.0001	ALLM > All other groups. Other groups similar.
DBP (mmHg)	83.9 $\pm$ 7* (82.4–85.3) 68–96	75.6 $\pm$ 8.8 (73.6–77.4) 54–98	80.8 $\pm$ 7.5 (79–83) 64–92	77.7 $\pm$ 8.5 (75–80.4) 64–90	<0.0001	ALLM > All other groups. Other groups similar.

ALLM: acclimatized lowland males; NHLM: native highland males; ALLF: acclimatized lowland females; NHLF: native highland female; EtCO₂: end-tidal carbon dioxide; SpO₂: oxygen saturation; Hb: hemoglobin; CaO₂: arterial oxygen content; SBP: systolic blood pressure; DBP: diastolic blood pressure.

* $p < 0.05$ is taken as significant (post hoc test Bonferroni).

Discussion

This study found differences in resting EtCO₂, SpO₂ and Hb in a large group of acclimatized lowland men and women, sojourning at 3300 m for several months, compared to native highlanders. The salient finding of this study is the presence of higher EtCO₂ in NHL, especially NHLM. These subjects were young and free of clinical disease, including clinical pulmonary and cardiovascular disease. Smoking has been shown to be associated with a significant widening of the arterial-end-tidal carbon dioxide tension and end-tidal-arterial oxygen tension, both at rest and exercise, in the absence of clinical disease.¹⁸ The higher EtCO₂ in smokers, in this study, compared to non-smokers, therefore implies a still greater PaCO₂ in these subjects. But, the higher EtCO₂ even in non-smoker NHLM compared to the other groups, suggests a physiological cause for this observation. At rest, EtCO₂ is usually 2.8 $\pm$ 1.6 mmHg lower than PaCO₂, which although a regulator of ventilation in normoxia, becomes a passive variable when ventilation is driven by significant hypoxia as at altitude.³ Further, there is evidence to suggest that ventilation in Himalayan native highlanders (NHL) is not responsive to CO₂, whereas in acclimatized lowlanders the hypercapnoeic ventilatory response (HCVR) is reset at altitude to maintain lower PaCO₂.^{2,19} Assuming equivalent metabolic production of CO₂, in a haemodynamically stable state at rest,

higher mean EtCO₂ in the NHL implies lesser mean ventilation. Ventilation-perfusion ratios and cardiac output, are two other variables that may determine delivery of CO₂ to the lung. But in subjects free of disease, these factors would not be relevant to determining CO₂ delivery and indeed it has been shown that acclimatized lowlanders have little, if any, change in ventilation-perfusion matching up to altitudes of 4600 m.²⁰ Resting cardiac output, too, returns to sea-level or slightly lower values, within days of arrival at HA.²¹ It is, therefore, likely that the higher EtCO₂ in NHL results from a reduced HVR. In a head to head comparison of the HVR in acclimatized lowlanders versus Himalayan highlanders (Tibetan and Ladakhi), Slesarev et al. have reported a lower HVR in the Himalayan natives.²² On the other hand, important metabolic differences exist in native highlanders and lowlanders. It has been reported that native highlanders have reduced utilization of beta-oxidation, greater omega-oxidation of lipids, greater efficiency of intermediary metabolism and oxidative phosphorylation and greater glucose metabolism in skeletal muscle. In lowlanders, fatty acids are the principal metabolic substrate in skeletal muscle at rest. On ascent to altitude, with acclimatization, metabolism becomes more dependent on utilization of glucose, displays downregulation of electron transfer complexes and tricarboxylic acid cycle enzymes, reduced fatty acid oxidation and improved oxidative phosphorylation coupling capacity with time.²³ These changes have, however, been studied over periods of one to two

months and reports that the lactate paradox (decreased exercise lactate production with increasing duration of stay in lowlanders) reverses with longer stay, suggest that studies to date may not have captured the entire spectrum of changes in metabolism on ascent to HA or in HA natives.²⁴ Considering that acclimatized lowlanders have reduced exercise capacity compared to highland natives, even after years of stay, it is unlikely that metabolism in lowlanders at HA ever duplicates that in natives. The respiratory quotient would, therefore, be expected to be greater always in natives of HA. This greater amount of CO₂ produced by natives for every unit O₂ consumed, couples with a ventilatory control system that does not respond to CO₂, could be another reason for the greater EtCO₂ observed in the NHL group in this study. The quantification of the greater respiratory quotient and its effect on PaCO₂, however, remains to be established. Resetting of ventilatory control to maintain lower PaCO₂ in acclimatized lowlanders could also, be a reason for the lower EtCO₂ in ALL.

The absence of gonadotropin stimulation of ventilation in NHLM is probably the reason why their EtCO₂ is greater than in NHLF. While it has been suggested that the HVR overrides gonadal hormone effects at altitude in acclimatized lowlanders, this may not be true for native highlanders.²⁵ Significantly increased ventilation in pregnancy in HA natives as also lowlanders, at altitude, is well documented.²⁶ Also, the reduced HVR in NHL may allow the effects of gonadal steroid to manifest. Wood et al. have reported greater EtCO₂ in native highland Ladakhi women at 3300 m than native highland Ladakhi men.⁶ The inclusion of older, post-menopausal women (age range 20–85 years) with reduced gonadotropin stimulation of ventilation, and a limited sample size of only 17 men at 3300 m (age range 20–81 years) in their study, is probably the reason for this difference in findings. The older age of their subjects also implies significantly longer exposure to smoke generated from bio-mass fuel, the principal fuel for cooking in Ladakhi rural households, and its consequence.

Oxygen saturation has been reported to be highest in Amhara Ethiopians, followed by Andeans, Tibetans and acclimatized lowlanders, although some studies suggest greater SaO₂ in lowlanders than Tibetans.^{21,27,28} The Ladakhis in this study had lower SpO₂ than the ALL. This difference in SpO₂ was however, principally due to the higher SpO₂ in ALLF; the ALLM, NHLM and NHLF having similar SpO₂. The greater SpO₂ in ALLF than in NHLF could be due to these two groups being in different phases of the menstrual cycle. Differences in levels of 2,3-Bi-phosphoglycerate and pulmonary diffusion capacity are known to occur with change in phase of menstrual cycle.^{29,30}

An attenuation of the haematopoietic response to hypoxia has been reported in Amhara Ethiopians, Tibetans and Ladakhis, such that their Hb at altitude is lower than that of acclimatized lowlanders.^{27,28,31} The NHL in this study, in contrast, had similar Hb as the ALL. Whether the lowland sojourners would have developed greater Hb with time, cannot be commented on, based on the findings of this study. Reynafarje et al. did report increase in Hb for 8 months followed by a plateau, in lowland soldiers stationed at 5650 m for one-year.³² The altitude in this study being significantly lower, may induce a more sluggish response especially if the ALL subjects had significant deficiency of iron and other

micronutrients.³³ On the other hand, the ALL may have achieved their full haematopoietic potential for 3300 m. Of note, with the existing ventilatory and hematological adjustments, the NHL and ALL achieved similar CaO₂ at rest.

The significantly greater heart rate and systemic blood pressure, both systolic and diastolic, seen in ALL is in consonance with cardiovascular changes known to occur with prolonged exposure to chronic hypoxia. Stroke volume decreases to below sea-level values with chronic hypoxia and there is a compensatory increase in heart rate to maintain cardiac output, which usually settles to below sea-level values, both at rest and during exercise in acclimatized lowlanders. Total peripheral resistance and systemic blood pressure increases, after an initial dip, due to sustained sympathetic overactivity.²¹ Sympathetic activity is believed to return to baseline over approximately 3 months of stay.³⁴ But few studies conducted over longer time frames, at greater altitudes, suggest that the increase in blood pressure over sea-level values is sustained for years.^{35–37} Fourteen percent of the NHL in this study were hypertensive in contrast to the 33% prevalence in rural areas of Leh district, reported by Norboo et al.³⁸ The difference is most likely due to the significantly greater age (60.1 years) of the subjects of the latter study. The 31.33% prevalence of hypertension in the lowland subjects of this study is, however, similar to the 29.8% for Asian Indians in the plains.³⁹ This is surprising in view of the younger age and normal BMI of the ALL subjects of this study. It would appear, that sojourn at 3300 m induces elevations of BP and indeed, causes hypertension in a significant number of sojourners, who might have been normotensive but for the sojourn at altitude. Future studies with larger sample sizes, lowland as well as highland controls and concurrent measurement of the multitude of factors involved in development of systemic hypertension should help shed more light on the role of environmental factors at HA in the development of this malady.

The impact of this study is limited by the absence of measurements at sea-level and direct measurement of HVR, HCVR and minute ventilation. In the absence of equipment to record these variables, we had to use EtCO₂ as a surrogate marker of ventilation and conjecture on the causes of the differences observed. Direct measurement of these variables is needed to establish the pattern of ventilatory adaptation/acclimatization to HA; ventilatory acclimatization being a pivotal response of the body on ascent to HA.

Alveolar ventilation appears to respond differently in natives and sojourners to the same hypoxic stimulus, whether men or women. Mechanistic studies of the oxygen delivery chain, including alveolar ventilation, gas exchange and transport kinetics and peripheral oxygen utilization in NHL and ALL could help us develop preventive strategies to ameliorate detrimental effects of long term stay at HA, such as cognitive decline and Chronic Mountain Sickness, conditions that are known to occur at altitudes above 2500 m.^{40–42}

Conclusion

Native highlanders, especially males, have a higher EtCO₂ and probably lower resting minute ventilation, than lowlanders

acclimatized over months to 3300 m. Blood hemoglobin and arterial oxygen content are, however, similar in natives and acclimatized lowlanders of the same sex. Resting heart rate and blood pressure are greater in healthy acclimatized lowlanders after months of stay at HA, compared to native highlanders.

Conflicts of interest

The authors have none to declare.

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Appendix A. Supplementary Table

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.mjafi.2018.03.008](https://doi.org/10.1016/j.mjafi.2018.03.008).

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