

Original Article

Altitude-related variations in heart rate variability among native Sikkimese: A cross-sectional study

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Background & objectives: Living at high altitudes causes chronic exposure to hypoxia, which triggers various physiological and autonomic adaptations, and many residents show successful acclimatization. Long-term exposure leads to time-dependent alterations in autonomic nervous system function, even in healthy individuals. Heart rate (HR) variability has long been a valuable tool for assessing autonomic activity, yet only a few studies have examined its association with altitude in healthy populations. This study assessed the impact of altitude on cardiac autonomic activity through HR variability analysis in healthy Sikkimese natives.

Methods: A cross-sectional study was conducted among the Sikkimese population residing at high, intermediate and low altitudes of Sikkim. Two areas from each altitude category were selected. Based on the population of the selected areas, the sample size was distributed using probability proportional to size, sampling. Systematic random sampling was then used to select participants. For each participant, a 5-min ECG was recorded using lead II of a Power Lab system. HR variability analysis was performed to derive time and frequency-domain indices from spectral analysis of successive R-R intervals.

Results: We found significantly higher values of time domain HR variability indices including standard deviation of all normal-to-normal intervals (SDNN) and root mean square of successive differences between normal heartbeats (RMSSD) among the people residing at higher altitudes in Sikkim ($P < 0.001$).

Interpretation & conclusions: Residents living at high altitudes exhibit enhanced parasympathetic cardiac activity compared to those residing at lower and intermediate elevations, reflecting a possible adaptive response to chronic hypobaric hypoxia.

Key words Autonomic nervous system - heart rate variability - high altitude - hypobaric hypoxia - Sikkim

High altitude (HA) is defined as an altitude greater than 2500 meters above sea level (mASL) or approximately 8200 feet¹. It is estimated that about 83 million people worldwide reside at elevations above 2500 mASL, primarily in South America, Central Asia, and Eastern Africa². The partial pressure of oxygen

decreases as altitude increases causing hypobaric hypoxia that drives acclimatization in sojourners and physiological adaptations in natives.

Living at high altitudes causes chronic exposure to hypoxia, which triggers various physiological and autonomic adaptations, and many high-altitude

residents show successful acclimatization. However, long-term exposure leads to time-dependent alterations in autonomic nervous system (ANS) function, even in healthy individuals³.

The ANS plays a vital role in regulating cardiovascular function and is influenced by both external factors (*e.g.*, environment, stress) and internal factors (*e.g.*, hormones). The parasympathetic and sympathetic discharge on the sinus node controls the heart rate. Increased parasympathetic stimulation causes a decrease in heart rate (HR), whereas increased sympathetic stimulation leads to an increase in heart rate.

One of the most reliable non-invasive markers of ANS function is heart rate (HR) variability, which reflects the cardiac sympathetic-vagal balance^{4,5}. It represents the variation in the time intervals between successive cardiac cycles. This variation of a healthy heart is complex and constantly changes in response to physiological and psychological challenges to maintain homeostasis. HR variability, measured from electrocardiogram (ECG) recordings, is an affordable, non-invasive, practical and reproducible measure and remains a gold standard technique for assessing autonomic regulation of the heart^{6,7}.

Hughson and colleagues reported that heart rate variability was reduced in three young adult males exposed to high altitude at day 4 and days 11 and 12 against that at sea level and persisted at this level during 12 days of exposure to high altitude. Little is known about the influence of chronic hypoxemia on cardiac parasympathetic regulation of heart rate in native highlanders⁸.

Despite extensive research on HR variability in clinical and physiological settings, studies examining altitude-related prolonged hypobaric hypoxia effects on HR variability among healthy individuals are limited⁹. Given Sikkim's unique topography, this study was conducted to evaluate the impact of altitude on autonomic function by analysing HR variability in healthy adult population residing at different altitudes.

Materials & Methods

This cross-sectional study was undertaken by the department of Physiology, Sikkim Manipal Institute of Medical Sciences, Gangtok, Sikkim, India from November 2023 to October 2024 after obtaining the ethical clearance from the Institutional Ethics Committee. Written permissions were also secured

from the *Panchayat*, Pipon (*Panchayat* equivalent in North Sikkim), and local councillor of the selected study regions. Written informed consent was obtained from all participants prior to inclusion in the study. The confidentiality of all data was strictly maintained, and participant anonymity was ensured throughout the research process.

Study design and setting: This cross-sectional study was conducted among healthy, permanent residents of Sikkim residing at varying altitudes. To investigate the influence of altitude on heart rate variability, participants were categorised into three altitude groups: low altitude (<1500 meters above sea level), intermediate altitude (1500–2500 mASL), and high altitude (>2500 mASL), based on the classification by Barry and Pollard (2003)¹⁰. To ensure geographic representation within each altitude category, two locations were randomly selected using the lottery method. This stratified approach helped ensure that the sample represented the broader population across different altitudinal zones of Sikkim.

Inclusion and exclusion criteria: Participants included healthy adult males and females who were born and brought up at their respective altitudes (thereby excluding migrants and re-entrants) and were willing to provide written informed consent. Individuals were excluded if they were chronic smokers (occasional smokers abstained for at least two hours before ECG recording), were on long-term medication for chronic illnesses such as cardiovascular or respiratory diseases, hypertension, or diabetes mellitus, were pregnant or within three months postpartum, had any acute illness at the time of data collection, or declined participation.

Sample size calculation and sampling strategy: This analysis is part of a larger project assessing both pulmonary function tests (PFT) and heart rate variability in native Sikkimese at different altitudes. As no prior HRV data were available for this population, the standard deviation of a PFT parameter from a previous altitude study¹¹, was used for sample size estimation to ensure adequate power. The same cohort was used for the present HR variability analysis. A relative error of 5 per cent, 95 per cent confidence interval (CI) and a potential attrition rate of 10 per cent was considered. The final estimated sample size was 350.

Two areas each from high altitude [Lachung (2700 m ASL) & Changu (3753 m ASL)], intermediate altitude [Sombaria (1530 m ASL) & Gangtok (1650 m ASL)], and low altitude [Singtam (426 m ASL)]

Table I. Descriptive demographic Parameters of Sikkimese population residing at three different altitudes

Demographic parameters		High altitude, n=100 (Mean±SD)	Intermediate altitude, n=188 (Mean±SD)	Low altitude, n=117 (Mean±SD)	Total, n=405 (Mean±SD)
Gender n (%)	Male	41 (41)	105 (55.9)	53 (45.3)	199 (49.1)
	Female	59 (59)	83 (44.1)	64 (54.7)	206 (50.9)
Age (in yr)		37.6±13.2	32.6±12.4	40.7±15.2	36.2±13.9
Height (in cm)		159.9±7.9	160.9±9.4	154.2±9.4	158.7±9.4
Weight (in kg)		67.0±12.7	62.8±11.4	61.1±10.3	63.4±11.6
BMI (kg/m ²)		26.2±4.4	24.3±3.8	25.7±4.0	25.2±4.1

& Chakung (1063 m ASL)] were selected by lottery. Population enumeration of each area was followed by participant allocation using probability proportional to size (PPS), reflecting the larger resident population at intermediate altitude compared to high and low altitudes. Consequently, the intermediate altitude group (n=188) had a larger sample than the high (n=100) and low (n=117) altitude groups. The electoral list served as the sampling frame; the first participant was chosen randomly, and the remainder systematically, to ensure unbiased recruitment.

HR Variability recording: To ensure the reliability of HR variability measurements, participants were instructed to abstain from consuming stimulant substances such as coffee, alcohol, tobacco, and cigarettes for at least two hours prior to ECG recording. A history of a good night's sleep was confirmed before the session. Participants were asked to take complete rest for at least 10 min before HR recording. During the recording, participants were advised to stay calm, relaxed, and avoid speaking. Recordings were carried out in a quiet room to minimize external disturbances, with proper skin preparation and removal of metallic jewellery, watches, and electronic devices.

ECG recordings were conducted for five min in a seated position using PowerLab equipment (AD Instruments), following the guidelines established by the 1996 'Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology'¹². Data were collected between 9 AM and 2 PM in schools, hospitals, and *panchayat* houses across the selected locations.

The ECG data were analysed offline using LabChart software, utilizing the HR Variability module, which extracts inter-beat (RR interval) variations. Parameters analysed included time-domain indices such as the standard deviation of normal-to-normal RR intervals (SDNN), the root mean square of successive RR

interval differences (RMSSD), and the percentage of consecutive RR intervals differing by more than 50 millisecon (pNN50). Frequency-domain measures included total power (TP), high-frequency (HF) power in the range of 0.15–0.45 Hz, low-frequency (LF) power in the range of 0.04–0.15 Hz, and the LF/HF ratio, representing the balance between sympathetic and parasympathetic activity.

Statistical analysis: Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Demographic variables were summarized by descriptive statistics. To examine the association of altitude on HR Variability parameters, one-way analysis of variance (ANOVA) was employed, followed by Bonferroni post hoc tests for multiple comparisons. *P* value of less than 0.05 (two-tailed) was considered statistically significant.

Results

A total of 405 healthy participants were included, comprising 199 males (49.1%) and 206 females (50.9%). The mean age of the participants was 36.2±13.8 yr (Table I).

The results indicated statistically significant differences in time-domain parameters like SDNN and RMSSD across the three altitude groups (Table II).

Pairwise comparisons between altitude groups showed that, in the time-domain analysis, SDNN and RMSSD values were higher in high-altitude residents than in both intermediate- and low-altitude residents. No meaningful differences were observed between the low- and intermediate-altitude groups. In the frequency-domain analysis, total power was higher in high-altitude residents compared with those at low altitudes, though the difference was small. Values in the intermediate group were similar to those in both the low- and high-altitude groups.

Table II. Comparison of HR variability parameters of Sikkimese population residing at high, intermediate and low altitudes

HRV parameters	High altitude, n=100 (Mean±SD)	Intermediate altitude, n=188 (Mean±SD)	Low altitude, n=117 (Mean±SD)	Total, n=405 (Mean±SD)	P value
NN Interval	758.4±83.6	748.5±94.7	762.4±96.0	755.0±92.4	0.4
SDNN	63.8±23.1	47.2±18.9	42.5±18.7	49.9±21.5	0
RMSSD	66.0±36.7	42.7±25.8	41.1±25.8	48.0±30.6	0
pNN50	13.1±15.1	15.0±15.8	11.6±14.0	13.6±15.1	0.15
Total power	4439.7±2404.4	3960.1±2502.2	3651.4±2342.5	3989.4±2444.1	0.05
LFP	29.1±1.0	29.7±11.9	29.9±10.8	29.6±11.1	0.85
HFP	37.1±17.4	35.2±17.8	32.2±16.5	34.8±17.4	0.11
LF:HF	1.27±1.33	1.3±1.4	1.3±1.0	1.3±1.3	0.93

NN, normal-to-normal; SDNN, standard deviation of all NN intervals; RMSSD, root mean square of successive differences between NN intervals; pNN50, percentage of successive NN intervals differing by more than 50 milliseconds; LFP, low-frequency power (0.04–0.15 Hz); HFP, high-frequency power (0.15–0.45 Hz); LF: HF ratio, ratio of low-frequency power to high-frequency power

Discussion

This study examined HR variability among healthy, permanent residents of Sikkim living at low (<1500 m), intermediate (1500–2500 m), and high altitudes (>2500 m), aiming to explore the chronic effects of altitude on cardiac autonomic regulation. We found significantly higher mean values of time-domain HR variability indices like SDNN and RMSSD in the high-altitude group, with a trend toward higher total power (TP) in frequency-domain analysis. Other indices such as pNN50, LF, HF, and LF/HF ratio did not differ significantly. These findings suggest that long-term residence at high altitude is associated with enhanced overall HRV and greater parasympathetic modulation.

These findings are consistent with those of Sharshenova *et al*¹³, who reported elevated SDNN, HF power, and TP in children living at moderate altitudes, and Malhotra *et al*¹⁴ who observed greater parasympathetic activity among high-altitude natives compared to acclimatized lowlanders. Bhattarai *et al*³ observed higher SDNN at rest and faster post-exercise recovery to resting phase, in highlanders, indicating more efficient autonomic regulation. Passino *et al*¹⁵ noted a predominance of high-frequency (HF) components in highlanders, while Boushel *et al*¹⁶ attributed the lower resting heart rate in acclimatized highlanders to enhanced parasympathetic neural tone.

In contrast, many studies investigating acute high-altitude exposure have documented opposite patterns, underscoring the importance of exposure duration. Oliveria *et al*¹⁷, in a systematic review showed that

acute hypoxia typically reduces HR variability by causing vagal withdrawal and sympathetic activation. Yuanyuan *et al*¹⁸ and Saito *et al*¹⁹ similarly observed decreased HRV indices and blunted autonomic responses during acute exposure in simulated hypoxic environments and trekking conditions. Studies in military personnel by Bhaumik *et al*²⁰ and in volunteers exposed to 4800 m by Roche *et al*²¹ also showed reduced parasympathetic activity and increased sympathetic drive, while Hughson *et al*²² noted elevated heart rates from adrenergic stimulation and parasympathetic withdrawal. Similar findings were also shown by Karinen *et al*²³, Zuzewicz *et al*²⁴ and Hainsworth *et al*²⁵.

Interestingly, studies tracking individuals over days (Bhaumik *et al*²⁰) found an initial drop in HRV and parasympathetic activity followed by partial recovery by day 5, indicating early stages of adaptation. Similarly, studies also report that with acclimatization, parasympathetic dominance is gradually regained (Cornolo *et al*²⁶). Farinelli *et al*²⁷ emphasized that acclimatization reduces sensitivity to sympathetic stimuli and shifts heart rate regulation toward vagal control. These findings illustrate that while acute hypoxia activates sympathetic drive, chronic exposure like the one in our study, promotes parasympathetic restoration and autonomic balance.

Other physiological studies also provide support for this transition from sympathetic to parasympathetic predominance with chronic altitude residence. Acute ascent has been associated with increased plasma and urinary catecholamine levels (Hornbein and Schoene⁸; Hoon *et al*²⁸; Von Euler and Hellner²⁹; Perini *et al*³⁰,

reflecting sympathetic activation. However, Wolfel and Levine³¹ observed catecholamine levels in lifelong highlanders similar to sea-level populations, suggesting downregulation of sympathetic drive with long-term exposure. Campos *et al*³² highlighted that acute hypoxic responses are typically sympathetic in nature, but longer exposure reduces adrenergic activity. These mechanisms are consistent with our findings of elevated SDNN, RMSSD, and TP, suggesting a stable parasympathetic predominance in high-altitude Sikkimese residents.

The higher HRV observed in our study suggests its potential as an objective marker of acclimatization. While the Lake Louise Score (LLS) remains the standard clinical measure for diagnosing acute mountain sickness, it is subjective. Recent evidence, including a meta-analysis by Tsai *et al*³³, indicates that HR variability indices such as pNN50 may predict altitude illness risk. Although we did not assess acute illness, the elevated SDNN and RMSSD in highlanders indicate successful long-term adaptation.

Our study has several strengths. It is among the few to assess HRV across multiple altitude categories in a relatively ethnically homogenous population (Nepali, Bhutia, Lepcha), minimizing genetic and cultural confounding. The inclusion of three altitude levels allowed a gradient analysis of autonomic patterns across elevations. However, certain limitations must be acknowledged. The sample size at high altitude was modest due to demographic constraints. We did not measure biochemical markers such as catecholamines or cortisol, which could have provided direct physiological corroboration of autonomic findings. Lastly, the design being cross-sectional, it excludes causal inference. Longitudinal studies could better establish whether altitude itself drives these differences. In conclusion, this study demonstrates that lifelong residence at high altitude among Sikkimese individuals is associated with enhanced HR variability, indicating parasympathetic predominance and successful autonomic adaptation to chronic hypobaric hypoxia.

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