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# Chemoreflex Mediated Arrhythmia during Apnea at 5050m in Low but not High Altitude Natives

**Running Head:** Apnea Induced Arrhythmia at Altitude

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**NEW AND NOTEWORTHY**

The peripheral chemoreflex increases both parasympathetic and sympathetic drive under chronic hypoxia. We found that this evoked brady-arrhythmias when combined with apneic periods in Lowlanders at altitude, which become relieved through supplemental oxygen. In contrast high altitude residents (Nepalese Sherpa) do not exhibit brady-arrhythmias during apnea at altitude through potential cardio-protective adaptations. The degree of bradycardia and brady-arrhythmias was related to the hypoxic ventilatory response, demonstrating that the chemoreflex plays an important role in these findings.

27

28 **ABSTRACT**

29

30 Peripheral chemoreflex mediated increases in both parasympathetic and sympathetic drive under chronic  
31 hypoxia may evoke brady-arrhythmias during apneic periods. We determined if: a) voluntary apnea  
32 unmasks arrhythmia at low (344m) and high (5050m) altitude, b) if high altitude natives (Nepalese  
33 Sherpa) exhibit similar cardiovagal responses at altitude; and c) if brady-arrhythmias at altitude are  
34 partially chemoreflex mediated. Participants were grouped as Lowlanders (n=14; age=27±6yrs) and  
35 Nepalese Sherpa (n=8; age=32±11yrs). Lowlanders were assessed at 344m and 5050m while Sherpas  
36 were assessed at 5050m. Heart rate (HR) and rhythm (Lead-II ECG) were recorded during rest and  
37 voluntary end-expiratory apnea. Peripheral chemoreflex contributions were assessed in Lowlanders (n=7)  
38 at altitude after 100% oxygen. Lowlanders had higher resting HR at altitude (70±15 vs. 61±15  
39 bpm;P<0.01) that was similar to Sherpas (71±5 bpm;P=0.94). High-altitude apnea caused arrhythmias in  
40 11 of 14 Lowlanders (junctional rhythm (n=4), 3° atrio-ventricular block (n=3), sinus pause (n=4)) not  
41 present at low altitude and larger marked bradycardia (nadir -39±18 bpm; P<0.001). Sherpas exhibited a  
42 reduced bradycardia response during apnea compared to Lowlanders (P<0.001) and did not develop  
43 arrhythmias. Hyperoxia blunted bradycardia (nadir -10 ±14bpm; P<0.001 compared to hypoxic state) and  
44 reduced arrhythmia incidence (3 of 7 Lowlanders). Degree of bradycardia was significantly related to  
45 hypoxic ventilatory response (HVR) at altitude and predictive of arrhythmias (P<0.05). Our data  
46 demonstrates apnea-induced brady-arrhythmias in Lowlanders at altitude but not in Sherpa (potentially  
47 through cardio-protective phenotypes). The chemoreflex is an important mechanism in genesis of brady-  
48 arrhythmias and the HVR may be predictive for identifying individual susceptibility to events at altitude.

49

**Key Words:** Hypoxia; Arrhythmia; Apnea; Sherpa; Chemoreflex

50

51

## 52 INTRODUCTION

53 It has been traditionally shown that efferent sympathetic and vagal outflow to the heart is reciprocal,  
54 through which increased activation of one pathway sees a respective decrease in the other (17). As such,  
55 the variation of cardiac sinus conduction is controlled through the balance between neural outflows in  
56 healthy populations. Concurrent increases in both pathways can occur under specific circumstances, and  
57 has previously referred to as cardiac “autonomic conflict” (29). This has previously been previously  
58 reported during periods of considerable autonomic stress (e.g. cold water submersion) due to conflicting  
59 activation of both sympathetic and parasympathetic pathways, ultimately promoting cardiac  
60 arrhythmogenesis in healthy individuals (8, 33). In addition, conflict can be seen to some degree in  
61 clinical populations suffering from sleep apnea, where elevated chemoreflex gain during apneic periods  
62 being is linked to both hypertensive and bradycardia responses (24, 30). Yet the degree of conflict can be  
63 considered minimal, with no previous accounts of arrhythmogenesis being noted in healthy populations  
64 exhibiting normal chemoreflex function during apnea (e.g. volitional breath holding).

65  
66 Heightened chemoreflex activity under chronic hypoxia results in a concurrent increase of efferent  
67 peripheral sympathetic nerve activity and cardiac vagal tone (9). However these increases are normally  
68 dampened by the inhibitor influence of pulmonary stretch receptors, ultimately blunting sympathetic  
69 outflow to heightened chemoreflex stress (19, 28, 31). As such, there is limited electrocardiographic  
70 evidence that suggests chronic hypoxia exposure leads to incidences of bradycardic arrhythmia within  
71 healthy individuals during sleep (4). The peripheral chemoreflex has been implicated specifically in these  
72 cases as the changes in heart rate observed appear correlated to the ventilatory response to acute hypoxia  
73 (22). Thus, there is a mechanistic basis for hypothesizing that chemoreflex sensitization during  
74 acclimatization at altitude (10) may promote autonomic conflict and potential bradycardic arrhythmic  
75 events during periods of sleep-related apnea. The use of voluntary apnea during chronic altitude exposure  
76 is therefore a relevant experimental model to investigate autonomic cardiac function independent of  
77 underlying comorbidities.

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Recently, we conducted a high altitude research expedition to 5050m in the Himalayan mountain range of Nepal. Our goal was to study autonomic function during chronic hypoxic exposure in Lowlanders. We contrasted these data with high altitude natives (Nepali Sherpa) to examine whether they would have similar vagal drive as Lowlanders, despite generations of residency at altitude. Our study was designed to experimentally investigate a) if voluntary apnea would unmask vagal mediated bradycardia or conduction abnormalities during wakefulness at altitude (5050m), b) the degree to which the peripheral chemoreflex plays a role in the susceptibility to bradycardic arrhythmia at altitude and c) if low and high altitude natives exhibit similar cardiovagal responses to apnea. Based on previous findings we hypothesized that voluntary apnea in the awake state would experimentally unmask heightened vagal activity and indications of autonomic conflict in Lowlanders at altitude, characterized by bradycardia and arrhythmias.

## **METHODS**

### ***Study Participants***

Fourteen Lowlanders (2 female; age=27±6yrs) and 8 highland Nepalese Sherpas (age=32±11yrs) from the Khumbu region of Nepal participated after providing informed written consent. All procedures were explained in English and Nepalese and approved by the University of Alberta Biomedical Research Ethics Board, the University of British Columbia Clinical Research Ethics Board, and the Nepal Health Research Council (Pro00064195) in compliance with the declaration of Helsinki. Health-history screening was negative for any pre-existing cardiovascular, respiratory or neurological disorders. Four Sherpa were current smokers (0.42±0.7 pack years).

104 ***Resting Baseline and Apnea Protocol***

105 Pre-expedition testing (Lowlanders) was conducted at 344m (Kelowna, Canada). After flying to  
106 2840m participants followed a conservative ascent profile (9-10 days) to the EV-K2-CNR research  
107 facility (5050m; Nepal). Two Lowlanders were administered medication for treatment of altitude illness  
108 during ascent (a single dose of acetazolamide (125mg) or dexamethasone), but were tested following a  
109 minimum 48hr washout period. Sherpa were tested on days 1-4 and Lowlanders were tested after 4-10  
110 days at 5050m. Both Sherpa and Lowlanders exhibited similar resting peripheral oxygen saturation (SpO<sub>2</sub>,  
111 82% and 83% respectively) at 5050m.

112  
113 Participants were tested in the supine position. ECG (Lead II) and arterial blood pressure (finger  
114 photoplethysmography; Finometer Pro, Finapres Medical Systems, Netherlands) were collected  
115 continuously at 1KHz (ADInstruments, Chart Pro v8.3.1). Brachial arterial pressure waveform was back  
116 calibrated through return to flow (RTF) correction confirmed against manual brachial measurements.  
117 Mean (MAP), systolic (SBP) and diastolic (DBP) pressures were calculated on a beat-by-beat basis from  
118 the calibrated pressure waveform. Beat-by-beat cardiac output (CO) was calculated using the Model Flow  
119 algorithm and used to calculate total peripheral resistance (TPR = MAP/CO). SPO<sub>2</sub> was continually  
120 assessed (pulse oximetry; Nellcor, Medtronic, USA). Following 10 minutes of quiet baseline measures  
121 participants were instructed to perform an end-expiratory apnea (at functional residual capacity). An  
122 investigator paced participants' breathing and signaled when to initiate apnea. Participants wore a nose  
123 clip and were instructed to "hold their breath for as long as possible". The role of the peripheral  
124 chemoreceptors was assessed in seven Lowlanders by repeating apnea at altitude after 1-2 min of pre-  
125 breathing 100% oxygen. In addition, individual hypoxic ventilatory responses (HVR;  
126  $\Delta$ Ventilation/ $\Delta$ SpO<sub>2</sub>) at altitude were recorded in a subset of Lowlanders within our study (n=11; 1  
127 female) and Sherpa (n=6) by breathing a fixed FiO<sub>2</sub> (~16%) for five minutes while at 5050m. However,  
128 this HVR response was only measured once and not during successive periods while at altitude. We were

129 unable to obtain the HVR response in three of the fourteen Lowlanders and two of the eight Sherpa.  
130 These HVR measures were performed independent of the study, though they were at similar time points.

131

### 132 *Data and Statistical Analysis*

133 In order to determine if voluntary apnea unmasks autonomic conflict in Lowlanders and Sherpa at  
134 altitude; values were calculated at two periods within each group (Lowlanders, lowlanders with  
135 supplemental oxygen, and Sherpa) and condition (low and high altitude). Baseline values were calculated  
136 over 5 minutes of spontaneous breathing. Electrophysiological characteristics (waveform amplitudes,  
137 durations and intervals) of the ECG were assessed during the 30 sec immediately preceding apneas;  
138 cardiac cycles (15-45) were over-laid, aligned with the R-wave and the aggregate was analyzed using  
139 automated software (Chart Pro 8.3.1). To account for variation in apnea duration, cardiovascular data  
140 from the final 10 cardiac cycles of each apnea were analyzed. A cardiologist (SVD) identified and  
141 classified conduction abnormalities from ECG waveforms from the 3 beats immediately preceding and 3  
142 beats following apnea breakpoint.

143

144 Baseline heart rate variability (HRV) was calculated during 5 minutes to contrast the relative  
145 contribution in sympathetic and parasympathetic activation between low and high altitude, and under  
146 supplemental oxygen at high altitude. HRV was analyzed using commercially available software  
147 (ADI, MLS310/8 HRV, Colorado Springs, CO, USA). Frequency domain analyses included  
148 spectrum analysis of very low (VLF; 0-0.04 Hz), low (LF; 0.04-0.15 Hz), and high (HF; 0.15-  
149 0.40 Hz) frequency bands. Temporal domain analyses included the standard deviations of the  
150 deviations between successive RR intervals (SDNN) and Root Mean Square of the Successive  
151 Differences (RMSSD). Total power was calculated as the variance of all NN intervals. The ratio  
152 of LF to HF power (LF/HF) was also used.

153



154 Statistical analyses was performed using Sigma Stat 3.13 (Systat Software, Chicago, IL). Results are  
155 reported as mean  $\pm$  standard deviation. Differences in cardiovascular data between conditions (low vs.  
156 high vs. high+ oxygen) and between groups (Lowlanders vs. Sherpa) were assessed using pre-planned  
157 contrasts (paired and unpaired T-tests). Mann-Whiney tests were run in incidences of non-normal  
158 distributions. Differences in incidence of arrhythmias between conditions in Lowlanders were assessed  
159 using McNemar's test for paired dichotomous data. In order to correct for multiple comparisons ( $c$ ), the *a*  
160 *priori* alpha ( $\alpha$ , 0.05) was adjusted ( $\alpha'$ ) using the experiment-wise error rate ( $\alpha_e$ ) (15, 32):

$$\alpha' = \frac{\alpha_e}{c}$$

$$\alpha_e = 1 - (1 - \alpha)^c$$

166 Relationships between measures were assessed using Pearson correlations. Receiver operating  
167 characteristic (ROC) curve analysis was performed to assess the specificity and sensitivity of an  
168 individual's HVR to predict the susceptibility to arrhythmia during apnea at altitude.

169

## 170 RESULTS

171 All 14 Lowlanders were successfully tested at 344m and 5050m. No sex differences were present  
172 between the 2 females in the Lowlander group. Prior to testing one Lowlander was categorized as having  
173 mild acute mountain sickness at altitude (Lake Louise score 3), but no other participants exhibited  
174 symptoms of illness.

175

176 Group characteristics and cardiovascular function for each condition are reported in Table 1. HR  
177 increased in Lowlanders at high altitude ( $p < 0.05$  vs. low altitude); becoming similar to Sherpas. SBP,  
178 DBP, MAP, CO, and TPR were unchanged in Lowlanders at high altitude (SBP  $P = 0.060$ ; DBP  $P = 0.782$ ;  
179 MAP  $P = 0.901$ ; CO  $P = 0.159$  and; TPR  $P = 0.056$ ) and no different than Sherpas (SBP  $P = 0.786$ ; DBP  $P =$

180 0.287; MAP P=0.641; CO P=0.581 and; TPR P=0.789). High altitude HVR was not different between  
181 Lowlanders (1.11± 1.78 L/min/% desaturation) and Sherpa (0.28± 0.16 L/min/ % desaturation; P=0.317).  
182 This remained non-significant even after accounting for one apparent Lowlander “outlier” with a high  
183 HVR (6.2 L/min/ % desaturation; P=0.242).

184

185

186 Ascent to altitude saw a shortening of the P-R interval (P<0.001) and P-wave duration (P<0.05), QRS  
187 complex widening (P<0.001), QTc prolongation (P<0.001) and P-wave amplitude depression (P<0.001)  
188 in Lowlanders (Table 2). Sherpas also exhibited widened QRS complexes (P<0.001) and longer QTc  
189 (P<0.05) at altitude compared to Lowlanders at low altitude (Table 2). The incidence of arrhythmia at  
190 rest was low in all groups and conditions (Table 3). One Lowlander exhibited periodic premature  
191 ventricular contractions during rest at both altitudes, but the incidence remained low (<2/min) and  
192 unchanged between altitudes. Upon ascent to altitude one Lowlander developed persistent junctional  
193 rhythm that was not relieved with oxygen. No arrhythmias were noted in Sherpa at rest.

194

195 Lowlanders saw no difference in indices of HRV (SDNN, RMSDD, and total power) between  
196 low and high altitude with exception to RRI, which became significantly decreased (1157± 240ms versus  
197 979±208 ms; P<0.001) at high altitude. However, oxygen supplementation did not relieve SDNN,  
198 RMSDD, total power, and RRI at altitude. Sherpas did not exhibit any difference in HRV measures to  
199 Lowlanders at high altitude. For all groups/altitude there was no difference in frequencies (VLF, LF, and  
200 HV) and total power. However, Lowlanders exhibited a significant increase in the LF/HF ratio at high  
201 altitude (P<0.05), while both the supplemental oxygen group and Sherpas LF/HF ratio was not different at  
202 altitude.

203

204

205 ***Responses to Voluntary Apnea at Low Altitude***

206 At low altitude, Lowlander SpO<sub>2</sub> was 98±1% prior to apneas but was not obtained during or  
207 immediately post-apnea. Lowlanders had an apnea duration of 30.4± 11.1s (range 15-74s) which resulted  
208 in a modest bradycardia response (-10±15 bpm; P<0.001) (Figure 1). No changes in ECG parameters  
209 were noted during apnea at low altitude, although 3 of the 14 Lowlanders developed arrhythmia  
210 (premature atrial contractions, atrial bigeminy, and non-conducted sinus beat; Table 3).

211

212 ***Responses to Voluntary Apnea at High Altitude***

213 At high altitude, resting SpO<sub>2</sub> was similar in Lowlanders (82±3%) and Sherpa (83±4%; P=0.933).  
214 Apnea resulted in further desaturation of Lowlanders (nadir 78±7%) and Sherpa (nadir of 75±5%;  
215 P=0.344 versus Lowlanders at altitude). Apnea duration was also reduced in Lowlanders [15.4±5.3 s  
216 (range 9-27s), P<0.001 compared to low altitude] that was similar to Sherpa (15.8±2.6; Range 12-19s).

217

218 Lowlander apneas saw magnified bradycardia at high altitude (-39± 18 bpm; P<0.001 versus low  
219 altitude). In contrast, Sherpa had a reduced extent of bradycardia during apnea (-7± 10 bpm; P<0.001  
220 versus Lowlanders). Despite bradycardia blood pressure progressively rose in Lowlanders to a peak MAP  
221 at low altitude (112± 19mmHg; P<0.001 versus baseline) and high altitude (100±21 mmHg P< 0.01  
222 versus baseline). Peak blood pressure response was similar in Sherpa (100± 12 mmHg; P=1.035 versus  
223 Lowlanders at altitude) (Figure 1). Between rest and apnea only QTc duration was significantly reduced  
224 (P<0.01) in Lowlanders. Apneas at high altitude resulted in a prolongation of the QRS (P<0.01) and PR  
225 intervals (P<0.05) while P and T wave amplitudes were depressed (P<0.001) in Lowlanders. Sherpas and  
226 Lowlanders exhibited mostly similar ECG values during apnea at altitude. However, Sherpa P-wave  
227 duration was significantly prolonged (P<0.05) compared to Lowlanders.

228

229 At high altitude there was a greater incidence in arrhythmias during apnea in Lowlanders (11 of 14;  
230 P<0.05) compared to low altitude apnea. Identified arrhythmias included sinus pause/arrest, junctional,

231 and 3° atrio-ventricular block (Figure 2; Table 3). In contrast, no abnormalities were apparent during  
232 apnea in Sherpas, despite no differences in the duration of apnea or degree of desaturation when  
233 compared with lowlanders at altitude.

234  
235 As HVR was similar between groups (see above), including the one female participant, data were  
236 combined to assess the relationship between HVR and heart rhythm. The gain of the bradycardic  
237 response during apnea across groups was correlated with HVR (Figure 3). Two Lowlanders were  
238 identified as statistical outliers using studentized residuals; however, the relationship remained significant  
239 when these individuals were either included or removed from the analysis (Figure 3). When data were  
240 grouped based on the presence or absence of arrhythmia during apnea, those individuals exhibiting apneas  
241 had significantly higher HVRs (Median 0.66 L/min) vs. those that did not exhibit arrhythmias (Median  
242 0.26,  $P < 0.02$ ; Figure 4a). ROC analysis further indicated that HVR was significantly predictive of the  
243 incidence of arrhythmia during apnea (AUC = 0.86,  $P < 0.05$ ; Figure 4b) with a sensitivity of 75% and  
244 specificity of 78% when using an optimized HVR cutoff of 0.40 L/min (Figure 4c). However, there was  
245 no relationship between HVR and the magnitude of bradycardia during apnea ( $R^2 = 0.08$ ).

246

#### 247 *Influence of Supplemental Oxygen to Apneic Response at High Altitude*

248 Supplemental oxygen was administered to 7 out of the 14 Lowlanders at high altitude prior to  
249 voluntary apnea. This increased initial SpO<sub>2</sub> from 82± 3 % to 96± 1 % ( $P < 0.001$ ) prior to apnea and  
250 reduced resting heart rate (62± 10 bpm;  $P < 0.05$  versus altitude). Apnea duration was prolonged (67.0±  
251 45.2 s;  $P < 0.01$  versus euoxic apnea) following oxygenation. Oxygenation significantly blunted apnea  
252 related bradycardia (Figure 1;  $P < 0.05$ ) but increased associated peak in MAP (117± 16mmHg;  $P < 0.05$ ).  
253 Supplementation of oxygen returned R-wave amplitude to low altitude values and the incidence of  
254 arrhythmia was significantly reduced compared to euoxic apnea (3 of 7 Lowlanders,  $p < 0.05$ ; Table 3).

255

256

257 **DISCUSSION**

258 In the current study we have demonstrated that through the use of voluntary apnea at altitude, there  
259 exists considerable underlying vagal and sympathetic drive in Lowlanders as marked by significant  
260 bradycardia and incidence of brady-arrhythmias. In contrast, Sherpas exhibited a less pronounced  
261 bradycardia during apnea and an absence of arrhythmias. Using supplemental oxygen we further  
262 demonstrated that the augmented bradycardia and arrhythmias observed in Lowlanders were specifically  
263 related to the peripheral chemoreflex. This was also supported by a significant relationship between the  
264 participant specific HVR and the degree of bradycardia occurring during apnea. Furthermore, ROC  
265 analysis indicated that heightened HVR was significantly predictive of the susceptibility to high altitude  
266 arrhythmias during apnea.

267

268 At altitude Lowlanders exhibited shorter P wave duration and PR Interval; as well as enlarged P and R  
269 wave amplitudes, suggesting an elevated sympathetic drive as seen previously (11, 14). In clinical  
270 contexts shortening of P and PR intervals is associated with increased risk of atrial fibrillation (1, 26).  
271 Despite changes in ECG conductance, arrhythmias during baseline were not observed in either  
272 Lowlanders or Sherpa. Previous accounts altitude related arrhythmias in Lowlanders have been reported.  
273 These have been primarily documented during periods of physical exertion after rapid ascent (3) or  
274 during sleep (4). Similar to our findings, these events were also associated with flattened T-wave  
275 amplitudes and p-wave shortening(3). Recently, Woods *et al.* (34) noted the presence of symptomatic  
276 sinus tachycardia at altitude (n=2) during periods of strenuous exercise via implantable loop recorder;  
277 where Brooks *et al.* (4) also noted arrhythmias during periods of exertion periods at altitude in 16  
278 Lowlanders using continuous ECG monitoring. In both reports, arrhythmia incidence was increased at  
279 higher altitudes (5000-7550m) as well as with longer exposure periods (4, 34). Both our data and these  
280 previous findings suggest high altitude to be a “pro-arrhythmia” environment, where the influence of  
281 hypoxia may be compounded further during periods of stress. Although we did not obtain continuous

282 ECG monitoring through the study; our findings agree with the presence of arrhythmias during periods of  
283 heightened stress.

284

285 Previous studies show increased periodic breathing and central apnea at altitude in Lowlanders (2, 5,  
286 27); as well as associated periods of bradycardia (16, 20, 22, 27) and arrhythmia (6, 16, 20). Thus, the  
287 current study utilized voluntary apnea to characterize the mechanisms of altitude related bradycardia and  
288 arrhythmia in Lowlanders at rest. The significant bradycardia as well as the development of arrhythmias  
289 (11 of 14 Lowlanders) during apnea is indicative of heightened sympathetic and parasympathetic  
290 innervation of the heart at altitude (9, 17, 25). Although the relationship sympathetic and  
291 parasympathetic control is often considered reciprocal, when both innervations are concurrently elevated  
292 the heart experiences what has previously been termed as “autonomic conflict”. The occurrence of cardiac  
293 arrhythmias during cold-water immersion has been attributed to this conflict (29) when high sympathetic  
294 (cold shock response) and parasympathetic (mammalian diving reflex) activity occurs. As classically  
295 described, the primary cardiovascular consequences of peripheral chemoreceptor activation are  
296 concurrently elevated sympathetic and parasympathetic activity (9). Yet under eupneic conditions  
297 hypoxia engages pulmonary reflexes (via the hypoxic ventilatory response) that inhibit both  
298 parasympathetic (9) and sympathetic activity (19, 28, 31). The degree of chemoreflex sensitivity and its  
299 direct relationship to sympathetic augmentation at altitude is not fully understood. Despite this, earlier  
300 works have demonstrated that the augmentation of sympathetic activity under acute hypoxia exposure is  
301 driven through heightened peripheral chemoreflex activation (23, 35). In the current study we have  
302 demonstrated a similar “autonomic conflict” that is unmasked during apnea and mediated via the  
303 peripheral chemoreflex. Firstly, we showed that the bradycardia associated with apnea at altitude was  
304 correlated with the hypoxic ventilatory response. Secondly, oxygen administration prior to apnea at  
305 altitude eliminated bradycardia and reduced the incidence of arrhythmia to the same level as observed at  
306 low altitude.

307

308           Although Sherpas had a similar breath hold duration and resting arterial oxygen saturation; they  
309 did not exhibit significant bradycardia or any arrhythmias. Previous data from native Tibetans indicate a  
310 normal ECG compared Han residents who had migrated during childhood to high altitude (13). We saw  
311 that breath holding generated arrhythmias in most Lowlanders but not Sherpa. Thus, these findings  
312 suggest that Sherpa exhibit an altered cardiac response to hypoxic stress. However, it is unclear what the  
313 specific nature of the adaptation that might be present. We do not believe this is related to differences in  
314 chemoreflex sensitivity as our findings are consistent with recent data indicating Sherpas to have similar  
315 chemoreflex sensitivity to acclimatized Lowlanders (7, 12, 36). Yet when Lowlanders and Sherpa were  
316 considered together, we found that high altitude HVR was significantly related to the normalized  
317 bradycardic response to high altitude apnea. Previously, Masuyama *et al.* (21) observed a significant  
318 relationship between low altitude HVR and high altitude sleep related (normalized) bradycardia. These  
319 previous data are intriguing as the relationship they demonstrate is apparent across conditions (low vs.  
320 high altitude) and sleep state (awake vs. sleep). This would suggest a robust predictive utility of low  
321 altitude HVR. In keeping with this, we demonstrated that high altitude HVR was significantly predictive  
322 of arrhythmias during apnea at altitude and therefore potentially useful as a predictor for risk of high  
323 altitude arrhythmia.

324

### 325 **Considerations**

326           The current study was apart of a larger research expedition to the Himalayan Range in Nepal and  
327 involved several independent studies examining vascular, cerebral auto-regulatory, neuromuscular, and  
328 autonomic function between Lowlanders and Sherpa. As such, certain time-dependent and technical  
329 limitations exist with regards to testing both Lowlanders and Sherpa at altitude. One limitation was the  
330 inability to repeat the supplemental oxygen trial within Sherpa. Sherpa were initially tested at 5050m and  
331 soon followed by Lowlanders. Yet significant arrhythmic events were only noted in Lowlanders at  
332 5050m. Following several examples of arrhythmias within Lowlanders we attempted to address the  
333 potential chemoreflex contribution though supplemental oxygen. However, Sherpa exhibited neither

334 considerable bradycardic responses nor arrhythmias during apnea. Therefore, we believe that  
335 supplemental oxygen would not have produced any considerable difference in cardiovagal responses  
336 during apnea.

337

338         We demonstrate a relationship between the HVR and degree of bradycardic response at altitude.  
339 However, we acknowledge that two individuals with high HVRs (statistically identified as outliers in  
340 relation to the rest of our participants) appear to weight this relationship. However, even if these two  
341 participants were removed, there still existed a significant relationship between HVR and bradycardic  
342 response (see figure 3). We acknowledge that our measure of HVR may exhibit some degree of  
343 ventilatory suppression through respiratory induced alkalosis, thus further minimizing central  
344 chemoreceptor activation. This limitation within our HVR measure should be considered during  
345 interpretation of results. However, our specific goal was to assess peripheral chemoreceptor contributions  
346 within a high altitude field setting. Due to the nature of the technique that was utilized for determining  
347 HVR (measuring the ventilatory response to continuous 16% FiO<sub>2</sub> at 5050m) without successive  
348 measurements; it would be recommended that utilizing HVR for predicting bradycardic events should be  
349 investigated further to confirm the present findings.

350

### 351 **Conclusion**

352         Our results suggest increased parasympathetic activity and sympathetic drive at altitude promote  
353 “autonomic conflict” during apnea. Thus, potential conflict may promote both cardiac changes and  
354 arrhythmia development in Lowlanders that travel to higher elevations for work or pleasure. Since high  
355 altitude HVR appears to be predictive of arrhythmia incidence; further evaluation of low altitude HVR  
356 should be evaluated for predicting the susceptibility of to high altitude brady-arrhythmia. The lack of  
357 arrhythmias in Sherpa suggests an adaptive mechanism, though it is unclear if the mechanism behind this  
358 response is due to generational adaptation.



359 **AUTHOR CONTRIBUTIONS**

360 The experiments within this study were conducted at both the Center for Heart, Lung, and Vascular  
361 Health (UBC Okanagan, Kelowna; Canada) and the EV-K2-CNR Research Facility (Lobuche; Nepal).  
362 Co-authors listed have contributed to either i.) conception or design of work (CDS, MS, JPM, and SAB),  
363 ii.) acquisition, analysis, or interpretation of data for the work (SAB, HD, FS, LR, LS, CDS, JPM, MS,  
364 and SVD), or iii.) drafting the work or revising it critically for important intellectual content (PNA, CKW,  
365 SAB, CDS, RH, JPM, and MS). All persons listed have qualified for authorship and approve of the final  
366 version of the manuscript. Finally, all authors listed agree to being accountable with regards to ensuring  
367 accuracy and integrity for the work currently investigated.

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372

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378

379 **DISCLOSURES**

380 The authors declare no conflicts of interest, financial or otherwise.

381

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482 **FIGURE LEGENDS**

483 **FIGURE 1.** Responses to apnea in Lowlanders at 344m (n.14; black circle), Lowlanders at 5050m (n.14;  
484 white circle), Lowlanders + O<sub>2</sub> at 5050m (n.7; blue circle), and Sherpa at 5050m (n.8; red circle). *Panel*  
485 *A*, Absolute bradycardia response to apnea. *Panel B*, Percentage change of bradycardic response to apnea.  
486 A significant bradycardia response was observed in Lowlanders at high (but not) low altitude. Apnea  
487 after 100% oxygen eliminated bradycardia in Lowlanders. Sherpa did not exhibit bradycardia during  
488 apnea at altitude. *Panel C*, Absolute pressor response during apnea. *Panel D*, Percentage change of  
489 pressor response during apnea. All data has been aligned to break-point and the last 10 cardiac cycles  
490 have been plotted. The mean nadir/peak responses are also identified. \*Lowlanders at high altitude  
491 significantly different from all other groups,  $P < 0.05$ ; † Significant difference between Lowlanders at low  
492 altitude vs. Lowlanders at high altitude,  $P < 0.05$ ; ‡ Significant difference between Lowlanders at low  
493 altitude and Sherpa,  $P < 0.05$ ; § Significant difference between Lowlanders + Oxygen (n.7) at altitude and  
494 Sherpa,  $P < 0.05$ ; || Significant difference between Lowlanders + Oxygen and Lowlanders (without  
495 oxygen) at altitude,  $P < 0.05$ .

496 **FIGURE 2:** Raw data demonstrating apnea induced arrhythmia at altitude. Examples of ECG tracings  
497 from the same male participant during apnea at low (top) and high altitudes (bottom). Apnea at altitude  
498 exhibited arrhythmic events, such as 3<sup>o</sup> heart block (see inset bottom right)

499 **FIGURE 3:** Correlation analysis between the normalized bradycardic response to apnea and hypoxic  
500 ventilatory response at altitude across groups. Closed circles represent Lowlanders (n.14) and open  
501 circles represent Sherpa (n.8). Two lowlanders were identified as statistical “outliers” (red symbols) based  
502 on studentized residuals. However, a significant relationship was also maintained if these participants  
503 were excluded (inset). The dashed lines and dotted lines represent the linear regressions and 95%  
504 confidence intervals respectively.

505

506 **FIGURE 4:** Hypoxic ventilatory response was higher in individuals who developed arrhythmias during  
507 apnea (A). Receiver operating curve analysis indicated that the hypoxic ventilatory response was  
508 significantly predictive of the incidence of arrhythmia at altitude (B). When an optimal cut-off was  
509 determined (0.40 L/min/% desaturation), the hypoxic ventilatory response was predictive of arrhythmias  
510 with a sensitivity of 75% and specificity of 78%.



**Table 1:** Demographic, cardiovascular, and sympathetic function in Lowlanders and Sherpa at low and high altitudes.

	<b>LOWLANDERS</b>			<b>SHERPA</b>
	334m (n =14)	5050m (n =14)	5050m +Oxygen (n =7)	5050m (n =8)
<b><i>Subject Demographics</i></b>				
Age (years)	27± 6	27± 6	30± 8	32± 13
Height (m)	1.77± 0.8	1.77± 0.8	1.79± 0.06	1.68± 0.08
Weight (kg)	72.2± 10.1	69.4± 8.6	69.3± 10.3	63.7± 10.1
BMI (kg/m <sup>2</sup> )	23.1± 2.8	22.2± 2.5	21.5± 2.9	22.8± 3.5
<b><i>Resting Cardiovascular Function</i></b>				
Heart Rate (bpm)	61± 15	70± 15*	62± 10*	71± 5‡
SPO <sub>2</sub> (%)	98± 1	82± 3	96± 1 †	83± 4
Systolic Pressure (mmHg)	119± 9	113± 13	113± 8	111± 9
Diastolic Pressure (mmHg)	66± 7	70± 10	71± 8	65± 8
Mean Pressure (mmHg)	84± 8	86± 11	89± 7	84± 9
Cardiac Output (L/min) ♦	5.9± 1.8	5.5± 1.4	5.1± 1.1	6.0± 1.7
Total Peripheral Resistance♦	15± 4	17± 4	19± 7	16± 7

♦ Values calculated using Model Flow.

\* Significantly different from Lowlanders tested at low altitude (334m); p <0.05.

† Significantly different from Lowlanders tested at high altitude (5050m); p <0.05.

‡ Significantly different from Lowlanders during hyperoxia (5050m + Oxygen); p <0.05.

**Table 2:** Electrocardiogram measurements made in Lowlanders and Sherpa at low and high altitudes during rest and apnea.

	<u>LOWLANDERS</u>			<u>SHERPA</u>
	334m (n =14)	5050m (n =14)	5050m +Oxygen (n =7)	5050m (n =8)
<b>REST</b>				
P-wave duration (ms)	96± 10	77± 20*	87± 12	97± 16†
P-wave amplitude (mV)	0.16± 0.05	0.14± 0.04	0.14± 0.06	0.11± 0.02*‡
PR-Interval (ms)	169± 19	124± 27*	146± 51	158± 38†
QRS duration (ms)	71± 14	121± 3*	119± 6 *	120± 1*
▲QTc (ms)	398± 26	456± 28*	449± 23 *	408± 15†‡
R-wave amplitude (mV)	1.76± 0.70	1.24± 0.60	1.49± 0.45 *	1.19± 0.22*
T-wave amplitude (mV)	0.49± 0.19	0.28± 0.14*	0.39± 0.19 *	0.36± 0.15*
<b>APNEA</b>				
P-wave duration (ms)	96± 20	74± 27	68± 22	68± 34†‡
P-wave amplitude (mV)	0.15± 0.05	0.10± 0.06*	0.10± 0.06*	0.09± 0.06*
PR-Interval (ms)	163± 31	128± 26*	151± 55	157± 37
QRS duration (ms)	74± 13	119± 4*	117± 5*	113± 10*
▲QTc (ms)	398± 34	410 ± 33§	417± 31*	465± 51‡
R-wave amplitude (mV)	1.67± 0.79	1.45± 0.74	1.65± 0.60*	1.25± 0.34
T-wave amplitude (mV)	0.48± 0.19	0.32± 0.18*	0.40± 0.28	0.37± 0.13

All measurements were taken using a standard lead II configuration. Measurements during apnea were taken from the 10 cardiac cycles prior to volitional breakpoint

▲Framingham correction (QT+0.154\*(1-RR).

\* Significantly different from Lowlanders tested at low altitude (334m); p <0.05.

† Significantly different from Lowlanders tested at high altitude (5050m); p <0.05.

‡ Significantly different from Lowlanders during hyperoxia (5050m +Oxygen); p <0.05.

§ Significantly different from rest within the same condition/group; p <0.05.

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**Table 3:** ECG conduction abnormalities identified at rest and during voluntary apnea.

	<b>LOWLANDERS</b>			<b>SHERPA</b>
	334m (n =14)	5050m (n =14)	5050m +Oxygen (n =7)	5050m (n =8)
<b>ABNORMALITIES IDENTIFIED AT REST</b>				
Premature Ventricular Contractions (< 2/min)	1	1	1	---
Junctional Rhythm	---	1	1	---
<b>ABNORMALITIES ASSOCIATED WITH APNEA*</b>				
Atrial Bigeminy	---	---	1	---
Premature Atrial Contractions	1	---	---	---
Ectopic Atrial Rhythm	1	---	---	---
Non-conducted Sinus Beat	1	---	---	---
Non-conducted sinus beat / Junctional Escape	---	1	---	---
Sinus Pause/Arrest	---	1	---	---
Sinus Pause/Arrest with Junctional Escape	---	2	---	---
Sinus Pause with Junctional Rhythm	---	1	---	---
Sinus Arrest with Junctional Rhythm	---	3	1	---
3° A-V Block	---	3	1	---

ECG assessment carried out by cardiologist (SVP) who was blinded to group and condition. Premature ventricular contractions were observed at rest in the same individual under all conditions; the rate of occurrence did not change with condition. One individual developed persistent junctional rhythm at altitude, this persisted during the oxygen administration.

\* All conduction abnormalities associated with voluntary apnea occurred immediately preceding or following (< 3 beats) break-point.

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# FIGURES

## FIGURE 1.

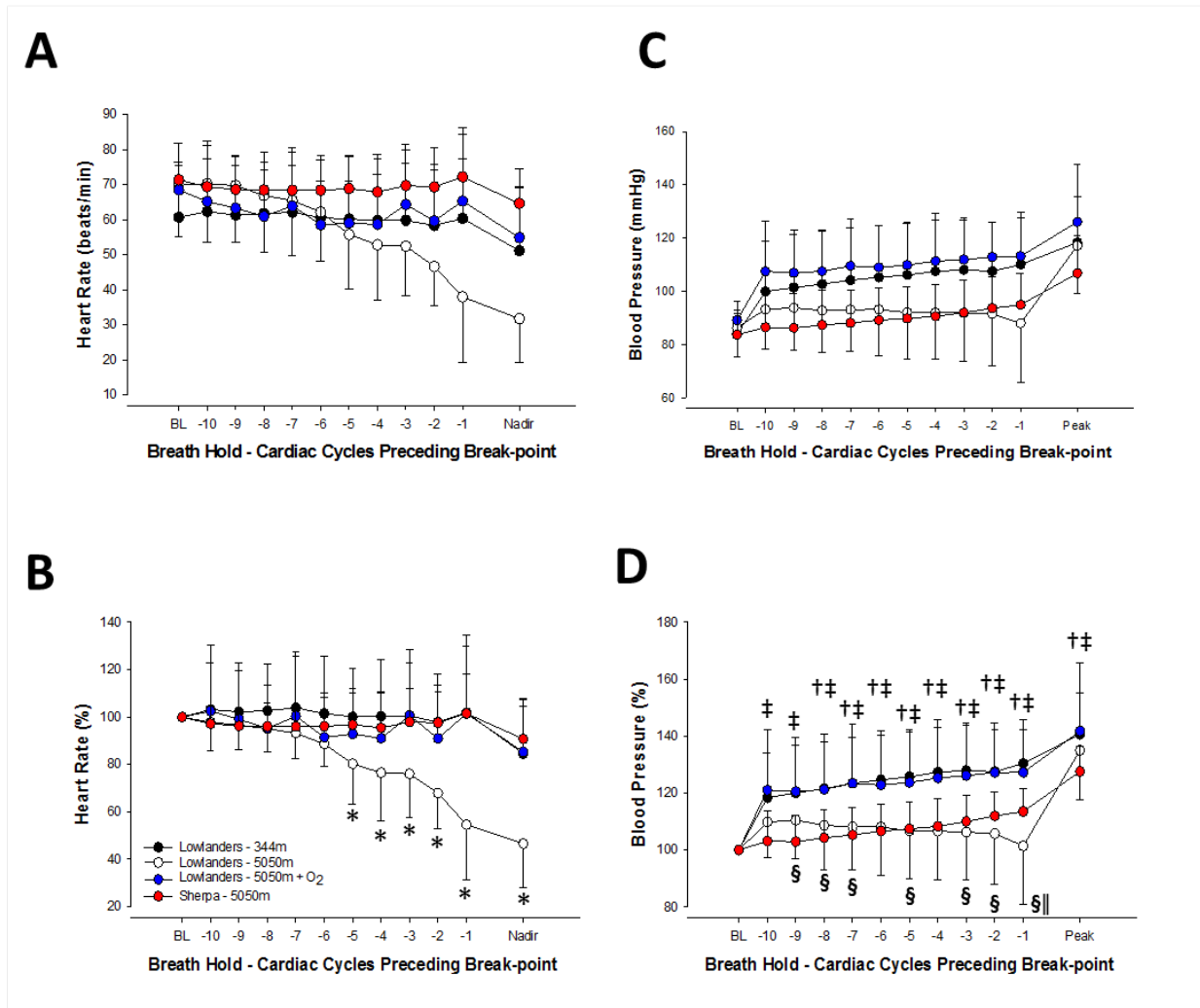


FIGURE 2

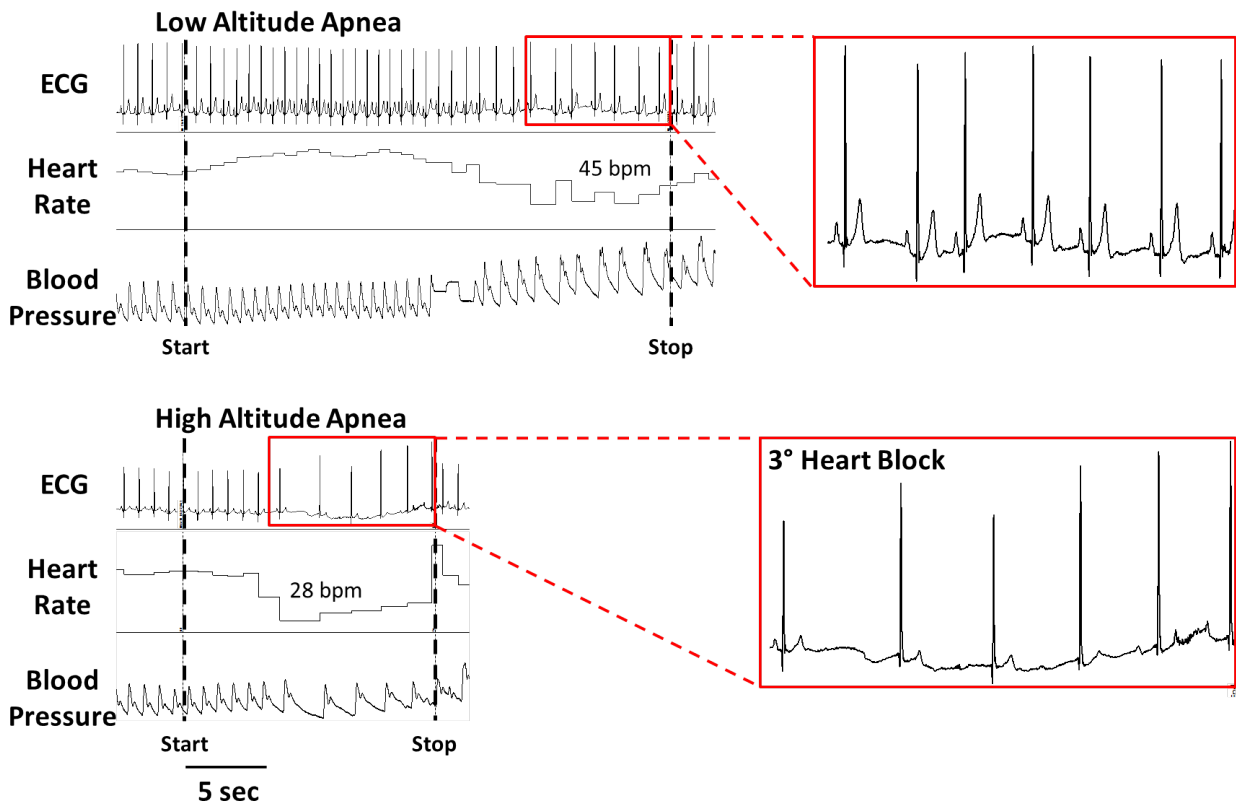


FIGURE 3.

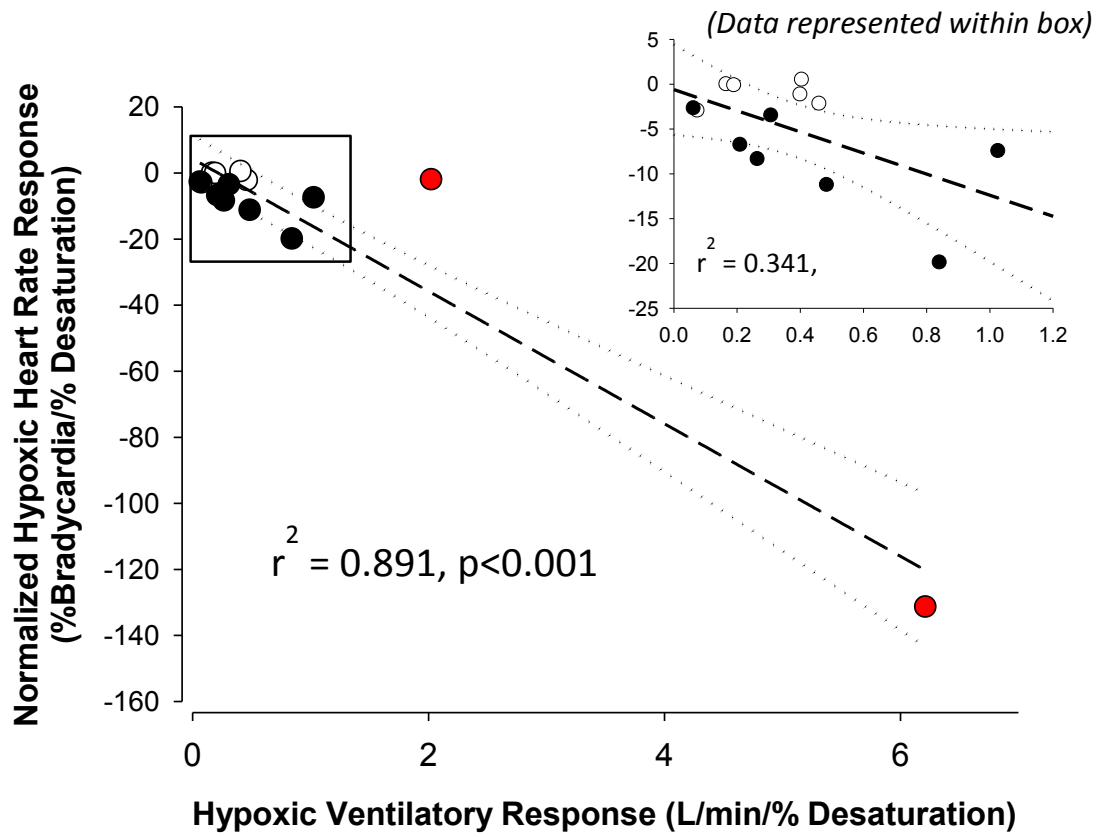


FIGURE 4

