



## Highs and Lows of Sympathetic Neuro-cardiovascular Transduction: Influence of Altitude Acclimatization and Adaptation

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1 Highs and Lows of Sympathetic Neuro-cardiovascular Transduction: Influence of  
2 Altitude Acclimatization and Adaptation

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54 **NEW & NOTEWORTHY** This study has identified that sympathetically mediated blood pressure  
55 regulation is reduced following ascent to high altitude. Additionally, we show that high altitude  
56 Andean natives have reduced blood pressure responsiveness to SNA outflow compared to  
57 Nepalese Sherpa. However, basal sympathetic activity is inversely related to the magnitude of  
58 SNA-mediated fluctuations in blood pressure regardless of population or condition. These data  
59 set a foundation to explore more precise mechanisms of blood pressure control under  
60 conditions of persistent sympathetic activation and hypoxia.

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64 **ABSTRACT:**

65 High-altitude (>2500m) exposure results in increased muscle sympathetic nervous activity  
66 (MSNA) in acclimatizing lowlanders. However, little is known about how altitude affects MSNA in  
67 indigenous high-altitude populations. Additionally, the relationship between MSNA and blood  
68 pressure regulation (i.e., neurovascular transduction) at high-altitude is unclear. We sought to  
69 determine 1) how high-altitude effects neuro-cardiovascular transduction and 2) whether  
70 differences exist in neuro-cardiovascular transduction between low and high-altitude  
71 populations. Measurements of MSNA (microneurography), mean arterial blood pressure (MAP;  
72 finger photoplethysmography), and heart rate (electrocardiogram) were collected in: I)  
73 lowlanders (n=14) at low (344m) and high-altitude (5050m), II) Sherpa highlanders (n=8;  
74 5050m), and III) Andean (with and without excessive erythrocytosis) highlanders (n=15;  
75 4300m). Cardiovascular responses to MSNA burst sequences (i.e. singlet, couplet, triplet, and  
76 quadruplets) were quantified using custom software (coded in MATLAB, v2015b). Slopes were  
77 generated for each individual based on peak responses and normalized total MSNA. High  
78 altitude reduced neuro-cardiovascular transduction in lowlanders (MAP slope: high-altitude,  
79  $0.0075 \pm 0.0060$  vs low-altitude,  $0.0134 \pm 0.080$ ;  $p=0.03$ ). Transduction was elevated in Sherpa  
80 (MAP slope,  $0.012 \pm 0.007$ ) compared to Andeans ( $0.003 \pm 0.002$ ;  $p=0.001$ ). MAP transduction  
81 was not statistically different between acclimatizing lowlanders and Sherpa (MAP slope,  $p=0.08$ )  
82 or Andeans (MAP slope,  $p=0.07$ ). When accounting for resting MSNA (ANCOVA), transduction  
83 was inversely related to basal MSNA (bursts/min) independent of population (RRI,  $r= 0.578$   
84  $p<0.001$ ; MAP,  $r= -0.627$   $p<0.0001$ ). Our results demonstrate transduction is blunted in  
85 individuals with higher basal MSNA, suggesting blunted neuro-cardiovascular transduction is a  
86 physiological adaptation to elevated MSNA rather than an effect or adaptation specific to  
87 chronic hypoxic exposure.

88

89 **INTRODUCTION:**

90 Sympathetic nervous system activity (SNA) has been shown to increase following exposure to  
91 high altitude in lowlanders (12, 17, 22, 26, 28, 39). The mechanism(s) governing persistent  
92 sympatho-excitation during hypoxic exposure remain unclear, but have previously been  
93 attributed to an increase in peripheral chemoreceptor drive (26, 31), elevated intracranial  
94 pressure (27), increased pulmonary artery pressure (29), or a combination of these factors.  
95 While heightened sympathetic outflow at altitude signals for global vascular constriction, mean  
96 arterial pressure (MAP) and total peripheral resistance (TPR) are maintained near sea level  
97 values during acclimatization (4, 28). This shift in communication between the nervous system  
98 and the vasculature (i.e., neurovascular transduction), indicates that there may be a reduction in  
99 the efficacy of SNA to effect vascular tone under conditions of prolonged hypoxia. The causes  
100 and consequences of this uncoupling remain poorly understood.

101       Of further interest are populations indigenous to high altitude, such as the Tibetan  
102 (Sherpa) and Peruvian (Andean) highlanders, who have been exposed to hypobaric hypoxia for  
103 millennia. Although there is considerable debate regarding specific durations at altitude, it is  
104 generally accepted that the Old World Plateaux (Ethiopian and Tibetan) have been settled for  
105 longer than the Altiplano in the New World (Andes) (1–3, 25, 43). This is suggestive that  
106 duration at altitude may play a role in the respective patterns of adaptation between high altitude  
107 populations. We have previously observed that Tibetan Sherpa show an overall lower degree of  
108 sympathetic activation compared to acclimatizing lowlanders, while having similar resting  
109 arterial pressure and similar or lower reactivity to heightened sympathetic stress (7, 28). In  
110 contrast, high altitude populations in the Andes exhibit a high reported incidence of excessive  
111 erythrocytosis (EE; defined as having a [Hb] >21g/dL in males, >19g/dL in females), which has  
112 been linked with vascular dysfunction and increased risk of cardiovascular disease (21, 35, 38).  
113 Interestingly, EE is extremely rare in Tibetan high altitude natives (38), suggesting distinct  
114 differences in the patterns of adaptation between these two high altitude populations.

*Phenotypic differences in neuro-cardiovascular transduction*

115 Differential adaption to long term hypoxic exposure between these two groups necessitates  
116 further investigation into mechanisms of cardiovascular control.

117         Although SNA and arterial pressure has been previously documented at altitude in both  
118 low and high altitude populations (3, 5, 7, 17, 22, 28), there is limited work that has investigated  
119 the transduction of sympathetic outflow to the integrated control of blood pressure in response  
120 to hypoxic exposure. Furthermore, there are no studies that have attempted to identify whether  
121 population-based differences exist in this aspect of sympathetic control. Thus, we aimed to  
122 characterize the relationship between spontaneous fluctuations in SNA to cardiovascular  
123 responses in North American and European lowlanders, Tibetan Sherpa, and Peruvian  
124 Andeans (both with EE+ and without EE). While renal adaptation and a shift in blood volume at  
125 high altitude also contribute to the integrated control of blood pressure, this study focuses on  
126 neuro-cardiovascular mechanisms. To address this, we analyzed muscle sympathetic nervous  
127 activity (MSNA) and simultaneous hemodynamic data collected during two previous high  
128 altitude research expeditions (Nepal 2016, and Peru 2018) to assess the impact of SNA on  
129 blood pressure regulation at rest. Our hypotheses were twofold: first, we hypothesized that  
130 lowlanders would show a blunted neuro-cardiovascular transduction response at high altitude  
131 compared to sea level. Second, we hypothesized that Sherpa would show a greater neuro-  
132 cardiovascular transduction response compared Andeans and acclimatizing lowlanders, due to  
133 previously observed (7, 28) lower reactivity to sympathetic stress.

134

135 **METHODS:**

136 Data for the current investigation was collected over two previous research expeditions to Nepal  
137 (UBC-Nepal Expedition; (42) and Peru (Global REACH 2018; (36). We have previously  
138 published on basal MSNA (28), and reactivity to exercise and breath-holding in the Sherpa (7).  
139 However, the analyses performed as part of this investigation address a specific novel  
140 hypothesis and report data not previously published. Specifically, the current study focuses on  
141 novel analyses related to the transduction of spontaneous fluctuations in SNA to mean arterial  
142 pressure (MAP) and heart rate (R-R Interval) responses over a ~10 minute baseline period.  
143 Although participants took part in a number of independent investigations during the above  
144 mentioned expeditions, care was taken to ensure that there was no overlap between studies,  
145 and each study addressed distinct *a priori* research questions.

146

147 ***Study Participants***

148 Participants were comprised of lowlanders (n=14; 27±1yrs; 2 female), Nepalese Sherpa (n=8;  
149 32±5yrs) and Peruvian Andeans (n=15; 42±3yrs). Note, the Andean group included 7 healthy  
150 (i.e. non-EE) and 8 EE men. Data were grouped for the healthy and EE Andeans since no  
151 differences in neuro-cardiovascular transduction were observed (details below). While  
152 demographics, resting hemodynamic function and basal metrics of MSNA have been published  
153 previously, these values are reported in Table 1 for completeness and context. Lowlanders,  
154 Sherpa, and Andean participants were free of any known respiratory, cardiovascular, metabolic,  
155 and neurological disorders as determined by a self-reported health history questionnaire. No  
156 participants were taking any medication at the time of testing. Lowlander participants were  
157 members of a larger expedition to Nepal in 2016 (42), and the Sherpa highlanders were  
158 recruited during the same expedition from the Khumbu Valley in Nepal. Pre-expedition testing of  
159 lowlanders was performed at 344 m (Kelowna, Canada), and then traveled to Nepal and  
160 ascended over 9-10 days to 5050m. Sherpa were not on any medication and were tested on



161 days 1-3 following arrival at 5050m, while Lowlanders were tested between days 1-10. Refer to  
162 Willie et al 2018 (39) for a more detailed description of ascent profiles.

163 Andean participants were recruited and tested as part of a second expedition (Global  
164 REACH 2018) (34) to Cerro de Pasco, Peru in 2018 (4300 m). Andeans with EE were  
165 diagnosed prior to being contacted and recruited using an existing local database (venous [Hb]  
166 concentration  $22.5 \pm 0.91$  g/dL). All Andeans were born above 3250m and were permanent  
167 residents of Cerro de Pasco.

168 High altitude residents provided informed written consent in their native language, with  
169 procedures explained in the local dialect as needed. Local Ethical approval was obtained for  
170 both expeditions by the University of Alberta Biomedical Research Ethics Board (Pro00064195  
171 and Pro00077330), Nepal Health Research Council, and Universidad Peruana Cayetano  
172 Heredia (#101686)

173

#### 174 **Data Collection**

175 All participants were tested in the supine position. All data were recorded and synced using  
176 Labchart (ADInstruments, Chart Pro v8.3.1, Australia). Heart rate (Electrocardiogram lead II),  
177 and the non-invasive arterial blood pressure waveforms (finger photoplethysmography;  
178 Finometer Pro, Finapres Medical Systems, Netherlands) were collected continuously at 1 KHz  
179 (ADInstruments, Chart Pro v8.3.1, Australia). Heart rate (HR) was calculated from the ECG R-R  
180 interval. Beat-by-beat mean arterial pressure (MAP), systolic (SBP) and diastolic (DBP)  
181 pressures were calculated from the arterial pressure waveform that was calibrated against  
182 manual sphygmomanometry (averaged from three separate readings) during rest. Beat-by-beat  
183 cardiac output (CO) was also calculated using the Model Flow algorithm and used to calculate  
184 total peripheral resistance ( $TPR = MAP/CO$ ) and conductance ( $TPC = CO/MAP$ ).  
185 Microneurography was used to directly measure muscle sympathetic nerve activity (MSNA). A  
186 tungsten microelectrode (200 $\mu$ m diameter, 35 mm long, tapered to a 1-5  $\mu$ m uninsulated tip)

187 was inserted percutaneous into the peroneal (common fibular) nerve, with an additional  
188 uncoated tungsten reference electrode inserted subcutaneously 1-3 cm from the recording site.  
189 The recording electrode was manipulated until a pulse-synchronous bursting pattern was  
190 identifiable in response to apnea but not a loud noise (16). The raw MSNA signal was acquired  
191 (Neuroamp EX headstage, ADInstruments; model 662C-3, Iowa University Bioengineering,  
192 USA), amplified (1000x pre-amplifier and 100x variable gain isolated amplifier), band pass  
193 filtered (700-2,000Hz), rectified, and integrated (decay constant 0.1s) to obtain a mean voltage  
194 neurogram. The Neuroamp was used to collect MSNA data during the 2018 Global REACH  
195 expedition; the model 662C-3 was used for MSNA data collection during the 2016 UBC-Nepal  
196 Expedition (at both low and high altitude). Both raw and integrated signals were sampled at 10  
197 KHz (ADInstruments, Chart Pro v8.3.1; Australia).

198

### 199 **Data Analysis**

200 MSNA bursts were identified using a semi-automated detection algorithm (Chart Pro 8.3.1) and  
201 confirmed by a trained observer (SAB/CDS) based on a pulse-synchronous pattern observed  
202 from both raw and integrated MSNA neurograms. Baseline MSNA was quantified as burst  
203 frequency (bursts/min) and incidence (bursts/100 heart beats). MSNA, peripheral oxygen  
204 saturation, and other cardiovascular metrics were extracted on a beat-by-beat basis for each  
205 individual over  $11 \pm 5$  minutes during baseline conditions at low altitude (lowlanders; 334m) and  
206 high altitude (lowlanders; 5050m, Sherpa; 5050m, Andeans; 4300m).

207 MSNA and hemodynamic variables for each individual were saved to Excel  
208 spreadsheets and read into custom software written in MATLAB (MATLAB 2015b; The  
209 MathWorks, Natick, Massachusetts) (32) to quantify the effect of neuro-cardiovascular  
210 transduction on measured hemodynamic parameters. The software identified MSNA burst  
211 locations via LabChart comment markers. Once identified, bursts were aligned with respect to  
212 the beat-by-beat data. Once aligned, MSNA was filtered to determine the position of all

213 recorded burst sequences consisting of single or consecutive groups of bursts separated on  
214 each side by 1 cardiac cycle without MSNA. Sequences consisting of singlet, couplet, triplet, or  
215 quadruplet (4 or more) bursts were grouped together for analysis (as per Steinback et al 2019)  
216 (32). Following the last burst in each sequence, the change in blood pressure, R-R interval and  
217 associated Finometer derived changes in cardiac output were tracked over the subsequent 15  
218 cardiac cycles, similar to the method described in previous studies (14, 15, 32). MAP, R-R  
219 interval and cardiac output data were used for analysis in order to comprehensively characterize  
220 systemic transduction. The mean change in MAP, R-R interval and cardiac output for different  
221 sequences was calculated by the software for each participant and saved to spreadsheets along  
222 with the standard deviation and number of burst sequences recorded. Peak changes in MAP, R-  
223 R interval and cardiac output were identified for each sequence type were subsequently  
224 grouped and overlaid to obtain a mean transduction for each participant (Figure 1) (32).  
225 Sequences of “non-bursts” were analyzed in a similar manner, with MAP, R-R interval and  
226 cardiac output indexed to sequences of cardiac cycles without bursts. To identify whether  
227 changes in R-R interval and cardiac output were directly associated with changes in MAP, we  
228 conducted a time to peak analysis for measures of MAP, R-R interval, and cardiac output.

229         Additionally, bursts were grouped into a quartile range (Q1-Q4) within each sequence,  
230 with Q1 representing the smallest summed amplitude of bursts, and Q4 being the largest  
231 summed amplitude within a given sequence. To account for individual differences in mean burst  
232 amplitude, burst amplitude was normalized to the mean summed amplitude within singlet Q1  
233 sequences (SQ1) which was set to 100% for each individual. All subsequent amplitudes for all  
234 quartiles were calculated as a percentage of SQ1. This normalization allowed for the  
235 comparison of quartile data between subjects and across groups. A mean transduction  
236 response for each individual was calculated as the slope of the peak responses in outcome  
237 plotted against the 16 normalized burst amplitude quartiles (i.e. 4 sequence types x 4 amplitude  
238 quartiles). Slopes were weighted (IBM SPSS statistics 25, United States, 2017) to account for

239 the number of occurrences (proportion) of quartiles within each sequence. Two Andean  
240 participants were excluded from the quartile analysis due to lack of data (<6 data points as  
241 opposed to 16; 4 sequences x 4 quartiles). The relationship between total normalized burst  
242 amplitude (per quartile) and physiological outcome (peak physiological response) is depicted in  
243 Figure 1. Individual slopes were then used to obtain a mean transduction response per group.  
244 As an additional analysis, we assessed the relationship between previously reported baroreflex  
245 gain data (28, 30) and the generated transduction slope.

246

### 247 **Statistical Analyses**

248 Comparisons were made between 1) lowlanders at low- and high-altitude, and 2) Sherpa,  
249 Andeans, and acclimatizing lowlanders. The dynamic relationship of transduction across cardiac  
250 cycles was compared within a given group using one-way ANOVAs. Holm-Sidak post-hoc  
251 analyses were conducted where main effect of group was identified. To assess the influence of  
252 changes in R-R interval on the MAP response, ANCOVA analyses were used, incorporating R-  
253 R interval as covariate. Between-group comparisons for lowlanders from low -to high-altitude  
254 were assessed using pre-planned contrasts (paired T-tests), with an adjusted alpha ( $\alpha'$ ) value  
255 corrected for multiple comparisons ( $c$ ). This was performed by adjusting the a priori alpha ( $\alpha$ ,  
256 0.05) using the experiment-wise error rate ( $\alpha_e$ ) (6, 18):

$$a' = \frac{a_c}{c}$$
$$a_c = 1 - (1 - a)^c$$

257

258 Alpha for comparisons between lowlanders at low and high altitude was corrected to  $p < 0.046$ .

259 Relationships between variables were evaluated using Pearson correlations and linear  
260 regression. To account for effect of resting MSNA on mean transduction responses, an  
261 ANCOVA analysis was run incorporating basal burst frequency as a covariate. Data are  
262 expressed as mean  $\pm$  standard deviation (SD) unless otherwise indicated. All statistical

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263 analyses performed using SigmaStat v14.0 (Systat Software). A p-value of <0.05 was  
264 considered statistically significant.

265

266

267 **RESULTS**

268 **Participant demographics and baseline metrics.** Participant demographics, baseline  
269 cardiovascular and MSNA metrics are reported in Table 1. Although lowlander and Tibetan  
270 Sherpa data have been reported elsewhere (6, 28), they are included in this novel analysis to  
271 enable comparison with Peruvian Andeans.

272 Andeans were older compared to lowlanders ( $p=0.001$ ) but not different to Sherpa.  
273 ( $p=0.065$ ). Andeans also had significantly elevated body mass index ( $\text{kg/m}^2$ ; BMI) compared to  
274 lowlanders and Sherpa ( $p=0.002$  and  $p=0.027$ , respectively). There were no significant  
275 differences in SBP, DBP or MAP in lowlanders at high and low altitude ( $p=0.07$ ,  $p=0.15$ ,  $p=0.26$ ,  
276 respectively). There were no significant differences between high altitude groups in SBP, DBP  
277 or MAP (main effects of  $p=0.871$ ,  $p=0.154$ ,  $p=0.773$ , respectively). Resting MAP was not  
278 significantly different between EE and non-EE Andeans ( $85\pm 2$  vs  $89\pm 8$  mmHg, respectively;  
279  $p=0.24$ ). Although Andean participants without EE appeared to have elevated burst frequency  
280 compared to Andeans with EE ( $44\pm 14$  vs  $37\pm 11$  bursts/min, respectively), these differences  
281 were not statistically significant (unpaired t-test;  $p=0.36$ ). Additionally, the mean transduction  
282 slopes for both MAP and RRI were not different between EE and non-EE Andean groups  
283 ( $p=0.35$  and  $p=0.60$ , respectively). Therefore, EE and non-EE participants were grouped  
284 together as Andeans for the subsequent analyses.

285 Representative burst patterns for all groups are shown in Figures 2. At high altitude,  
286 lowlanders had significantly elevated MSNA burst incidence and frequency ( $p<0.001$ ) compared  
287 to low altitude. Despite Sherpa being tested at a higher altitude than Andeans (5050m vs  
288 4330m), Sherpa had significantly lower burst frequency than Andeans ( $p=0.006$ ), as well as  
289 lower burst incidence compared to both lowlanders and Andeans ( $p=0.036$  and  $p=0.001$ ,  
290 respectively). Elevated burst frequency was associated with a lower proportion of single burst  
291 sequences and an elevated proportion of multiple burst sequences in both lowlanders at high  
292 altitude and Andeans (Figure 3). Conversely, lower burst frequency corresponded with a higher

293 proportion of singlet sequences and lower proportion of multiple burst sequences in lowlanders  
294 at low altitude and Sherpa (Figure 3).

295

296 ***The impact of high altitude on neuro-cardiovascular transduction in lowlanders***

297 ***Cardiac and pressor response to burst sequences.*** Changes in MAP following MSNA  
298 sequences were greater at low compared to high altitude in lowlanders for both singlet ( $2.2 \pm 1.1$   
299 vs  $0.83 \pm 0.58$  mmHg;  $p < 0.001$ ) and couplet ( $4.2 \pm 2.0$  vs  $1.8 \pm 1.6$  mmHg;  $p = 0.005$ ) sequences,  
300 but not different for triplet and quadruplet sequences ( $p = 0.699$ ;  $p = 0.547$ , respectively).  
301 However, the nadir in MAP following triplet and quad non-burst sequences was greater in  
302 lowlanders at high altitude ( $p = 0.041$  and  $p = 0.001$ ; Figure 4).

303 Following SNA bursts, there was an acute cardio-acceleration (decrease in R-R interval)  
304 occurring within 5 cardiac cycles. There were no significant differences between lowlanders at  
305 low and high altitude in decrease in R-R Interval across any burst sequence (singlets,  $p = 0.575$ ;  
306 couplets,  $p = 0.69$ ; triplets,  $p = 0.56$ ; quad,  $p = 0.30$ ). Following non-burst sequences, there was an  
307 acute cardio-deceleration (increase in RR interval). There were no differences between  
308 lowlanders at low versus high altitude in the R-R interval response to non-burst sequences  
309 (Figure 5).

310 ***Mean Transduction Slope.*** Mean transduction slope was greater in lowlanders at low  
311 altitude for R-R interval (low altitude,  $0.00017 \pm 0.00014$ ; high altitude,  $0.00007 \pm 0.00008$ ;  
312  $p = 0.032$ ). The transduction slope for MAP was blunted at high altitude (MAP slope,  
313  $0.0075 \pm 0.0060$  at high altitude versus  $0.0134 \pm 0.0080$  at low altitude;  $p = 0.03$ ). To examine the  
314 influence of altered basal SNA on transduction, an ANCOVA was run including resting MSNA  
315 (burst frequency) as a covariate. This analysis subsequently indicated no difference between  
316 low and high altitude for R-R interval or MAP slopes ( $p = 0.718$  and  $p = 0.278$ ; ANCOVA).

317 ***Differences in neuro-cardiovascular transduction between Sherpa, Andeans, and***  
318 ***acclimatizing lowlanders***

319           **Cardiac and pressor response to burst sequences.** Following bursts of MSNA,  
320 Sherpa showed a greater MAP response compared to Andeans ( $p < 0.001$ ) and lowlanders at  
321 high altitude ( $p = 0.010$ ) across all sequence types (main effect of group,  $p < 0.001$ ; Figure 4).  
322 Acclimatizing lowlanders showed a greater MAP response to MSNA bursts compared to  
323 Andeans ( $p < 0.001$ ). The drop in MAP (nadir) following non-burst sequences was greatest in  
324 lowlanders at high altitude (main effect of group,  $p = 0.017$ ; Figure 4). Subsequent post hoc  
325 analyses indicated that the overall fall in pressure following non-burst sequences appeared  
326 greater, but was not statistically different between lowlanders and Sherpa ( $p = 0.152$ ) but was  
327 greater in lowlanders compared to Andeans ( $p = 0.017$ ) (Figure 4).

328           The decrease in R-R interval following burst sequences was different between groups  
329 (main effect of group,  $p < 0.001$ ; Figure 5). Sherpa showed a greater drop in R-R interval  
330 compared to Andeans ( $p = 0.003$ ) but this was not statistically different to lowlanders ( $p = 0.051$ ).  
331 However, lowlanders exhibited a greater decrease in R-R interval compared to Andeans  
332 ( $p < 0.001$ ) across all burst sequences. The cardio-deceleration (decrease in R-R interval) was  
333 not difference between groups following non-burst sequences ( $p = 0.129$ ) (Figure 5).

334           **Mean Transduction Slope.** Using quartiles data, a main effect of group was identified  
335 for both MAP and R-R interval mean transduction slopes ( $p = 0.04$ ;  $p = 0.006$ , respectively; Figure  
336 6 & 7). Sherpa had a significantly greater slope for both MAP ( $0.012 \pm 0.007$ ) and R-R interval  
337 compared to Andeans (MAP,  $0.0031 \pm 0.0024$ ; R-R Interval,  $0.00003 \pm 0.00004$ ) ( $p = 0.003$  and  
338  $p = 0.005$ ) and a greater R-R interval slope compared to lowlanders ( $p = 0.046$ ). While Sherpa  
339 tended to have a greater MAP transduction slope compared to lowlanders this was not  
340 statistically significant ( $p = 0.08$ ). Lowlanders were not different from Andeans for R-R interval  
341 slope ( $p = 0.201$ ) or MAP slope ( $p = 0.07$ ).

342           The peak transduction in MAP was inversely related to prevailing degree of sympathetic  
343 activity, independent of group ( $r = -0.627$ ,  $p < 0.001$ ; Figure 6). Peak transduction in R-R Interval  
344 was also inversely related to prevailing sympathetic activity independent of group ( $r = 0.578$ ;



345  $p < 0.001$ ). Subsequent analysis indicated that mean transduction slopes were no longer  
346 significantly different between groups for either MAP or R-R interval slopes ( $p = 0.160$ ;  $p = 0.203$ ,  
347 respectively) when concurrent SNA burst frequency was taken into account as a covariate  
348 (ANCOVA).

349 ***Time to peak responses***

350 ***Time to peak in lowlanders.*** Time to peak was assessed in all groups for cardiac  
351 output (CO), MAP, and R-R Interval. At low altitude, changes in MAP occurred  $5.6 \pm 1.9$ s  
352 following burst sequences; changes in R-R Interval occurred  $2.1 \pm 1.0$ s following bursts;  
353 changes in CO occurred  $2.4 \pm 1.0$ s following bursts. Peak MAP responses followed both peak  
354 R-R interval ( $p < 0.001$ ) and peak changes in CO ( $p < 0.001$ ). Time to peak in R-R Interval and CO  
355 were similar ( $p = 0.46$ ). At high altitude, peak changes in MAP ( $4 \pm 2$ s) also followed peak  
356 changes in both R-R Interval ( $1.9 \pm 1.1$ s) and CO ( $2.9 \pm 1.1$ s) ( $p < 0.001$ ). Again, time to peak  
357 changes in R-R Interval and CO were similar ( $p = 0.23$ ).

358 ***Time to peak in Sherpa and Andeans.*** In Sherpa, time to peak change in MAP ( $4.6 \pm$   
359  $2.5$ s) followed peak changes in both CO ( $2.4 \pm 1.3$ s) and R-R interval ( $2.1 \pm 1.5$ ) ( $p < 0.001$ ).  
360 Time to peak for CO and R-R interval were similar ( $p = 0.56$ ). In Andeans, time to peak changes  
361 in MAP ( $3.1 \pm 2.5$ s) also followed peak changes in CO ( $1.8 \pm 1.0$ s) and R-R interval ( $1.3 \pm 1.0$ )  
362 ( $p < 0.01$ ). Time to peak was similar between CO and R-R interval ( $p = 0.17$ ).

363

364 **Discussion**

365 The purpose of the current investigation was to characterize the transduction of spontaneous  
366 bursts of MSNA to cardiovascular outcomes in low and high-altitude populations. The main  
367 findings were: 1) lowlanders exhibited a blunted neuro-cardiovascular transduction slope at high  
368 altitude compared to sea level, but had a greater drop in blood pressure during non-burst  
369 sequences; 2) Tibetan Sherpa showed an elevated transduction response compared to  
370 Andeans, who had consistently blunted neuro-cardiovascular transduction; 3) the increase in  
371 blood pressure following bursts of sympathetic activity was inversely related to prevailing levels  
372 of MSNA independent of population (ANCOVA,  $p < 0.001$ ). Andeans (EE+ and EE-), who had the  
373 highest resting values for burst frequency and incidence, consistently demonstrated a blunted  
374 pressure (MAP) and heart rate (R-R interval) response to burst sequences compared to other  
375 groups (Figures 4 & 5). Conversely, Sherpa showed greater vascular (MAP) and cardiac (R-R  
376 interval) responses to burst sequences despite significantly lower resting SNA, indicating an  
377 elevated transduction (Figures 4 & 5). These findings imply that neuro-cardiovascular  
378 transduction is an inverse function of resting sympathetic activity, and thus may be  
379 representative of a broader physiological adaptation to maintain normotensive pressure.  
380 Alternatively, alterations (elevation or decrease) in the level of sympathetic signaling may be  
381 required to compensate for blunted or heightened vascular responsiveness to vasoconstrictor  
382 signals. Further interventional studies are required to delineate these mechanisms.

383

384 ***The impact of high altitude on neuro-cardiovascular transduction in lowlanders***

385 Our findings demonstrate that transduction was blunted in lowlanders at high altitude.  
386 This may be attributable to specific physiological changes which occur in response to hypoxic  
387 exposure. Exposure to acute hypoxia is associated with a vasodilatory response (9, 23) which  
388 may be balanced by the concomitant sympatho-excitatory response (20). The dilatory influence  
389 of hypoxia may be reflected as the greater fall in pressure in non-burst sequences. The current

390 findings demonstrate that the nadir pressor response (MAP) following non-burst sequences was  
391 greater in lowlanders at high altitude (specifically for triplets and quadruplets+; Figure 4),  
392 supporting the idea that an opposing dilatory response offsets the vasoconstrictor effects of  
393 sympathetic activity following sympathetic bursts. This is supported by previous literature  
394 documenting the influence of vasodilatory pathways on vascular function in lowlanders (9), and  
395 concurs with the notion that the increase in sympathetic nervous system in response to hypoxia  
396 may mask a greater hypoxic vasodilation (23). Additionally, it could be interpreted that the  
397 elevation in SNA in acclimatizing lowlanders occurs to offset the influence of hypoxia mediated  
398 vasodilation and hence act to preserve arterial pressure. Furthermore, a shift to a greater  
399 proportion of larger burst sequences (Figure 3) may be beneficial in offsetting hypoxic  
400 vasodilation. Maintaining oxygen delivery in conditions of hypoxic stress while modulating  
401 sympathetic outflow to defend against hypotension represents a complex homeostatic  
402 interaction in the control of blood pressure.

403

404 ***Differences in neuro-cardiovascular transduction between Sherpa, Andeans, and***  
405 ***acclimatizing lowlanders***

406 Our results indicate that neuro-cardiovascular transduction is greatest in Sherpa  
407 whereas transduction was overall blunted in the Andeans, with acclimatizing lowlanders falling  
408 in the middle of these two populations. Despite differences in resting MSNA between groups,  
409 (with Sherpa exhibiting low activity and Andeans exhibiting highest levels of activity), all groups  
410 displayed similar values for blood pressure. Taken together, these findings indicate that the  
411 inverse relationship between neuro-cardiovascular transduction and sympathetic activity is likely  
412 an adaptive mechanism to maintain normal blood pressure. Previous work in patients with  
413 obstructive sleep apnea showed that higher resting sympathetic outflow in the absence of  
414 blunted transduction resulted in an elevation in blood pressure, suggesting that unaltered  
415 vascular transduction may contribute to the development of hypertension (33). Conversely, we

416 have demonstrated a blunted transduction during healthy pregnancies that appears to offset  
417 sympathetic hyperactivity and maintain blood pressure (32). This supports our interpretation that  
418 an adaptive resetting of neuro-cardiovascular transduction is an important response to maintain  
419 normotensive pressure.

420         It has been previously reported that transduction is inversely related to sympathetic  
421 baroreflex gain in young males (19). We have previously shown that there is an upward resetting  
422 of the baroreflex upon ascent to high altitude, while Sherpa appear to have a lower baroreflex  
423 operating point compared to acclimatizing lowlanders (28). Additionally, baroreflex operating  
424 point has been reported to be similar between EE+ and EE- Andeans (30). Considering the  
425 interaction between blood pressure control of SNA (baroreflex) and SNA control of blood  
426 pressure (transduction), it is possible that baroreflex sensitivity may be an important regulatory  
427 factor in the capacity of the cardiovascular system to buffer fluctuations in SNA. However, in a  
428 subsequent analysis of our data we did not observe a relationship between previously reported  
429 baroreflex gain values (28, 30) and transduction slope in the groups studied (lowlanders 344m,  
430  $r = -0.02$ ; lowlanders 5050m,  $r = -0.2$ ; Sherpa,  $r = 0.7$ ; Andeans,  $r = -0.2$ ). The incongruity between  
431 our findings and those previously published by Hissen et al (2019) may arise due to differences  
432 in methodological quantification of transduction. However, based on our current analyses,  
433 sympathetic baroreflex gain does not appear to be related to the transduction response.

434         While renal adaptation and shift in blood volume over time at altitude may contribute to  
435 control of blood pressure, our analyses focus specifically on acute neuro-cardiovascular control.  
436 The mechanism(s) by which transduction is altered between high altitude groups remains  
437 unclear. There may be a change in alpha adrenergic sensitivity or density to account for level of  
438 MSNA in order to mitigate the magnitude of changes in pressure. Under resting conditions, tonic  
439 sympathetic control over vascular tone is mediated primarily by noradrenaline binding to alpha 1  
440 and 2 adrenergic receptors (10, 13). Changes in this distribution (i.e., changes in sensitivity or  
441 receptor density) over time at high altitude may account for differences in neuro-cardiovascular

442 transduction. This is supported by studies documenting a blunted vasoconstrictor response to  
443 direct adrenergic stimulation in conscious rats following 4 weeks of hypoxic exposure (11, 24).  
444 Although vascular sensitivity was not assessed in the current study, it has been previously  
445 reported that healthy individuals at sea-level with higher resting MSNA demonstrate lower  
446 vascular responsiveness to adrenergic stimulation, indicating that there is an offsetting of MSNA  
447 at the level of the vasculature (8). Reduction in vascular sensitivity to MSNA could explain  
448 blunted transduction in Andeans, who exhibited the highest resting sympathetic activity despite  
449 having similar blood pressure to other groups. Reduced vascular sensitivity may be a  
450 physiological adaptation to higher resting sympathetic outflow. Alternatively, it could be  
451 interpreted that sympathetic outflow increases to account for low vascular sensitivity.  
452 Additionally, differences in noradrenaline release, uptake, or degradation at the level of the  
453 nerve terminal could contribute to the observed differences in the blood pressure response to  
454 sympathetic outflow. The precise mechanisms underlying blunted (or elevated) transduction  
455 have yet to be explored.

456         While our results indicate that the blunting (or elevation) in neuro-cardiovascular  
457 transduction is related to prevailing sympathetic activity, phenotypic differences may in turn  
458 drive the variation in resting sympathetic activity. Sherpa have been previously characterized as  
459 having lower basal sympathetic activity but a greater vascular responsiveness to sympathetic  
460 vasomotor drive compared to acclimatizing lowlanders (28). Thus, elevated transduction may be  
461 a physiological mechanism acting in concert with lower resting sympathetic activity to maintain  
462 vascular tone. Conversely, certain high altitude Andean populations have been characterized to  
463 exhibit impaired endothelial function (34, 38). It has previously been suggested that heightened  
464 sympathetic nerve activity may contribute to endothelial dysfunction (37); whether the systemic  
465 vascular dysfunction is related to elevated MSNA in the Andeans is not clear, but possible  
466 (although there are other factors that have been identified as a potential driver of impaired  
467 vascular function, such as EE) (35). (34, 38). Poor endothelial functional and/or lowered nitric

468 oxide (NO) bioavailability may contribute to a differential regulation of blood pressure in this  
469 group. However, the absence (or reduction) of a vasodilatory signal to offset transduction would  
470 likely result in a larger, rather than smaller, transduction response. In the current study, the  
471 Andean group demonstrated a consistently blunted transduction response, suggesting that  
472 decreased endothelial function and mechanisms of transduction are acting independently of  
473 each other. Further work is needed to elucidate the relationship between vascular function, SNA  
474 and neuro-cardiovascular transduction in these populations.

475         Although some form of sympathetic pathology related to vascular dysfunction may be  
476 expected to be more prevalent in Andeans with EE as opposed to non-EE, we did not observe  
477 any differences in our initial analysis of transduction (for both MAP and R-R interval) between  
478 these groups, indicating that both groups have blunted transduction despite notable  
479 hematological differences. While non-EE participants appeared to have elevated burst  
480 frequency compared to EE participants, these differences were not statistically significant  
481 ( $p=0.36$ ). However, this may be attributable to low sample size within the current data set  
482 (participants with EE,  $n=8$ ; non-EE,  $n=7$ ). Post hoc power analysis revealed low power for burst  
483 frequency (0.3). Based on calculated effect size for the current analysis (0.56), 41 participants  
484 would be required in each group to detect significant differences in MSNA burst frequency.  
485 Future studies should aim to include a larger cohort in order to specifically characterize  
486 pathology and neuro-cardiovascular transduction between EE and non-EE individuals.

487

## 488 **CONSIDERATIONS**

489 There are several considerations that should be recognized when interpreting our findings. First,  
490 due to differences in basal MSNA, the proportion of single versus multiple bursts was different  
491 across groups (Figure 3), resulting in a reduced sample size across burst sequences in groups  
492 with lower resting MSNA (specifically for triplet and quad+ sequences). However, a transduction  
493 slope was generated for each individual and scaled to the individual's SQ1 (Figure 1), and the

494 generated relationships were linear regardless of dropout in higher (i.e., triplet, quad+) quartiles.  
495 Additionally, each individual slope was weighted to account for the number of occurrences for  
496 each sequence. Therefore, we believe our data are still representative of transduction across  
497 individuals.

498         While we interpreted transduction to be an inverse relationship to resting sympathetic  
499 activity, there remains a possibility that a ceiling effect of MSNA exists, in which elevated  
500 bursting may not allow for vascular relaxation between bursts or groups of bursts (32). Lack of  
501 vascular relaxation between burst sequences could result in pressure remaining elevated  
502 following bursts, leading to an interpretation of apparent loss of transduction in groups with  
503 higher resting burst incidence (31). However, as previously discussed, vascular adrenergic  
504 sensitivity has been shown to be inversely related to resting MSNA (8); this strengthens our  
505 interpretation that populations who exhibit higher MSNA have an adaptive reduction in vascular  
506 sensitivity to, and thus a true blunting in their neuro-cardiovascular transduction rather than a  
507 limitation of our analysis.

508         We recognize that the use of local or total vascular conductance would be highly  
509 relevant in characterizing the effect of SNA on cardiovascular tone. However, there are some  
510 methodological considerations and limitations in incorporating these measurements. Firstly,  
511 there are methodological limitations of collecting continuous vascular flow data during the field  
512 studies. We were unable to collect sufficient continuous flow data in all locations or participants  
513 to make meaningful comparisons of local vascular conductance. Second, cardiac output  
514 variations calculated from ModelFlow have not been validated in the populations or conditions  
515 (prolonged hypoxia) of interest. We also recognize that in the current analysis we cannot  
516 discern how differences in blood volume, contractility, afterload, stroke volume, and cardiac  
517 output may affect the observed transduction (pressor) response. However, previous studies on  
518 neuro-cardiovascular transduction have assessed blood pressure as a key cardiovascular  
519 outcome using similar methodology to ourselves (14, 15, 32, 41). In these studies, using mean

520 arterial pressure as an index of vascular tone did not influence the interpretation of differences  
521 in neuro-cardiovascular transduction between groups or conditions. Thus, we believe that our  
522 analysis of changes in mean arterial pressure (MAP) are still relevant in determining how a  
523 given sympathetic stimulus affects cardiovascular function.

524 Our analysis of changes in R-R interval following burst sequences hinges on the  
525 assumption that cardiac sympathetic activity is related to peripheral MSNA. Additionally, acute  
526 alterations in heart rate could be interpreted as vagal withdrawal. However, the relationship  
527 between burst sequences and the R-R interval response are consistent with what would be  
528 expected for increases in sympathetic activity, i.e. R-R interval decreases (heart rate increases)  
529 following bursts of sympathetic activity in an apparent dose (increasing sequence length and  
530 burst amplitude; Figure 1) dependent manner. Additionally, in attempt to address whether  
531 sympathetically mediated effects on heart rate corresponded to concurrent changes in cardiac  
532 output, we conducted time to peak analyses in each group for measures of MAP, R-R interval,  
533 and finometer derived cardiac output (CO). This analysis revealed that peak changes in BP  
534 followed (by ~2-3s) the peak changes in both CO and R-R interval in all groups, while time to  
535 peak between CO and R-R interval were similar. This finding suggests that changes in heart  
536 rate are associated with concurrent changes in cardiac output. However, the dissociation of the  
537 time to peak between heart rate (and cardiac output) and blood pressure also confirms the  
538 distinct vascular influence of SNA on the observed BP response.

539 In this study, the Andean participants were significantly older compared to lowlanders;  
540 this could be a contributor to higher prevailing MSNA, as MSNA has been previously reported to  
541 be elevated in older populations (40). Additionally, Andean participants had a greater BMI  
542 compared to both Sherpa and lowlanders. However, the novel finding of this study is that SNA is  
543 inversely correlated with transduction; therefore, although age and/or BMI may account for  
544 higher resting SNA, our findings remain relevant in understanding blood pressure control across  
545 populations exhibiting sympathetic hyperactivity. Additional ANCOVA analyses revealed that



546 when both age and BMI were taken into account, burst frequency remained significant ( $p=0.013$   
547 and  $p=0.034$ , respectively) as was mean transduction slope (age,  $p=0.005$ ; BMI,  $p=0.005$ ).

548

## 549 **PERSPECTIVES**

550 In the current study we have demonstrated that sympathetic neuro-cardiovascular  
551 transduction is inversely related to resting levels of MSNA. Our data indicates that there is a  
552 downregulation (or upregulation) of vascular sensitivity to MSNA based on the prevailing level of  
553 signaling. Thus, we suggest that although there are adaptive differences between populations,  
554 blood pressure responsiveness to sympathetic outflow is representative of a broader  
555 physiological adaptation to maintain control of blood pressure, rather than a consequence  
556 specific to hypoxic exposure. Alternatively, MSNA could be increased in order to maintain  
557 vascular resistance and therefore blood pressure in cases of blunted vascular responsiveness.  
558 Future analysis should incorporate direct adrenergic stimulation or blockade in order to isolate  
559 whether this adapted response is mediated by the vasculature (i.e., down-regulation of  
560 sensitivity) or neural outflow (i.e., increased MSNA to account for level of sensitivity).  
561 Additionally, experimental studies should directly assess the influence of heightened SNA on  
562 transduction over time.

563

564

565 **AUTHOR CONTRIBUTIONS**

566 LFB and CDS contributed to the conception of the study. GMF and CDS contributed to  
567 conception and development of the analytical approach. GMF wrote the analysis software.  
568 CKW, MMT, VF, PNA, MS, JPM and CDS contributed to the design and conduct of the  
569 experiments carried out as part of the 2016 and 2018 expeditions. LFB, LLS, ERV, SAB, ARS,  
570 VLM, JSL, RJF, GAV, CG, MS, JPM and CDS contributed to the acquisition and or analysis of data.  
571 LFB, GMF, LLS, ERV, SAB, ARS, VLM, JSL, RJF, GAV, FV, CG, MMT, PNA, MS, JPM, and CDS  
572 contributed to the interpretation of data and the writing and critical revision of the manuscript.  
573 All authors approved the final version of the manuscript submitted for publication and agree to  
574 be accountable for all aspects of the work. All persons included as an author qualify for  
575 authorship, and all those who qualify for authorship are listed.

576 **COMPETING INTERESTS**

577 None

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732 **FIGURE CAPTIONS**

733 **Figure 1.** Example figure of quartile data. Representative bursts for a given quartile (Q1, Q2,  
734 Q3, Q4) within each burst sequence type (singlets, couplets, triplets, quad+). Bursts are scaled  
735 (LabChart) to mean burst amplitude for each participant. Burst size (i.e., normalized amplitude)  
736 and number of bursts (i.e., sequence) increases linearly with the magnitude of the physiological  
737 (outcome variable) response. Peak responses (Y axis) to burst sequences were identified within  
738 the 15 cardiac cycles (X axis) following a sequence. This quantification of transduction is  
739 indicative of how varying levels of neural activity influence the pressor response. This  
740 relationship was assessed in each individual participant and then used to obtain a mean  
741 transduction slope per group.

742 **Figure 2.** Integrated muscle sympathetic nerve activity signal over 30 seconds of baseline.  
743 Bursts are scaled (LabChart) to mean burst amplitude for each participant. Individual signal is  
744 representative of each group. A: Lowlander at low altitude (344m); B, same lowlander  
745 participant at high altitude (5050m); C, Sherpa (5050m); D, Andeans (4380m). Average burst  
746 frequency (bursts/min), burst incidence (bursts/100 heart beats), MAP (mmHg), HR (bpm),  
747 represented for each individual.

748 **Figure 3.** Percentage of total activity within a given sequence (singlet, couplet, triplet, quad+)  
749 per group. Data are represented as mean  $\pm$  SD. A: Lowlanders at low altitude (singlets, n=14;  
750 couplets, n=14; triplets, n=8; quad+, n=6). B: Lowlanders at high altitude (singlets, couplets,  
751 triplets, n=14; quad+, n=13). C: Sherpa at 5050m (singlets, couplets, triplets, n=8; quad+, n=5).  
752 D, Andeans at 4380m (singlets, n=15; couplets, triplets, quad+, n=14). Andeans with diagnosis  
753 of excessive erythrocytosis (EE) are depicted by gray circles.

754 **Figure 4.** Change mean arterial pressure (MAP; mmHg) following burst sequences (Panel A)  
755 and non-burst sequences (Panel B). Data are represented as mean  $\pm$  SD. Panel A: Lowlanders  
756 at low altitude (singlets, couplets, n=14; triplets, n=8; quad+, n=6), Lowlanders at high altitude  
757 (singlets, couplets, triplets, n=14; quad+, n=13), Sherpa (singlets, couplets, triplets, n=8; quad+,

758 n=5), Andeans (singlets, n=15; couplets, triplets, quad+, n=14). Panel B: Lowlanders at low  
759 altitude (singlets, couplets, triplets, n=13; quad+, n=14), Lowlanders at high altitude (singlets,  
760 couplets, quad+, n=14; triplets, n=13), Sherpa (n=8), Andeans (singlets, n=15; couplets, n=13;  
761 triplets, n=11; quad+, n=9). Andeans with diagnosis of excessive erythrocytosis (EE) are  
762 depicted by gray circles. Sherpa showed significantly elevated pressor response following burst  
763 sequences compared to lowlanders at high altitude ( $p=0.010$ ) and Andeans ( $p<0.001$ ) (Panel  
764 A). Lowlanders at high altitude had a significantly greater drop in pressure following non burst  
765 sequences compared to at low altitude ( $p<0.001$ ) and compared to Andeans ( $p=0.017$ ) (Panel  
766 B).

767 **Figure 5.** Change R-R interval (RRI; s) following burst sequences (Panel A) and non-burst  
768 sequences (Panel B). Data are represented as mean  $\pm$  SD. Panel A: Lowlanders at low altitude  
769 (singlets, couplets, n=14; triplets, n=8; quad+, n=6), Lowlanders at high altitude (singlets,  
770 couplets, triplets, n=14; quad+, n=13), Sherpa (singlets, couplets, triplets, n=8; quad+, n=5),  
771 Andeans (singlets, n=15; couplets, triplets, quad+, n=14). Panel B: Lowlanders at low altitude  
772 (singlets, couplets, triplet, n=13; quad+, n=14), Lowlanders at high altitude (singlets, couplets,  
773 quad+, n=14; triplets, n=13), Sherpa (n=8), Andeans (singlets, n=15; couplets, n=13 triplets,  
774 n=11; quad+, n=9). Andeans with diagnosis of excessive erythrocytosis (EE) are depicted by  
775 gray circles. Lowlanders and Sherpa had a greater drop in R-R Interval following burst  
776 sequences compared to Andeans ( $p<0.01$ ;  $p=0.02$ ) (Panel A).

777 **Figure 6.** Mean transduction slope for arterial pressure (MAP; mmHg) plotted against burst  
778 frequency (bursts/min). Individual slopes are weighted in order to account for proportions of  
779 bursts within each sequence. Panel A, Lowlanders at low (344m) altitude (n=13),  $r= -0.67$ ; B,  
780 Lowlanders at high (5050m) altitude (n=14),  $r= -0.65$ ; C, Sherpa at high (5050m) altitude (n=8),  
781  $r=-0.53$ ; D, Andeans at high (4300m) altitude (n=13),  $r= -0.69$ . Andeans with diagnosis of  
782 excessive erythrocytosis (EE) are depicted by gray circles. Data fitted to linear regression

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783 model; 95% confidence interval. Pearson correlation coefficient ( $r$ ), R squared ( $r^2$ ) and p value  
784 are reported for each group.

785 **Figure 7.** Mean transduction slope for R-R interval (s) plotted against burst frequency. Individual  
786 slopes are weighted in order to account for proportions of bursts within each sequence. Panel A,  
787 Lowlanders at low (344m) altitude (n=14); B, Lowlanders at high (5050m) altitude (n=14); C,  
788 Sherpa at high (5050m) altitude (n=8); D, Andeans at high (4300m) altitude (n=13). Andeans  
789 with diagnosis of excessive erythrocytosis (EE) are depicted by gray circles. Data fitted to  
790 exponential decay function for regression.

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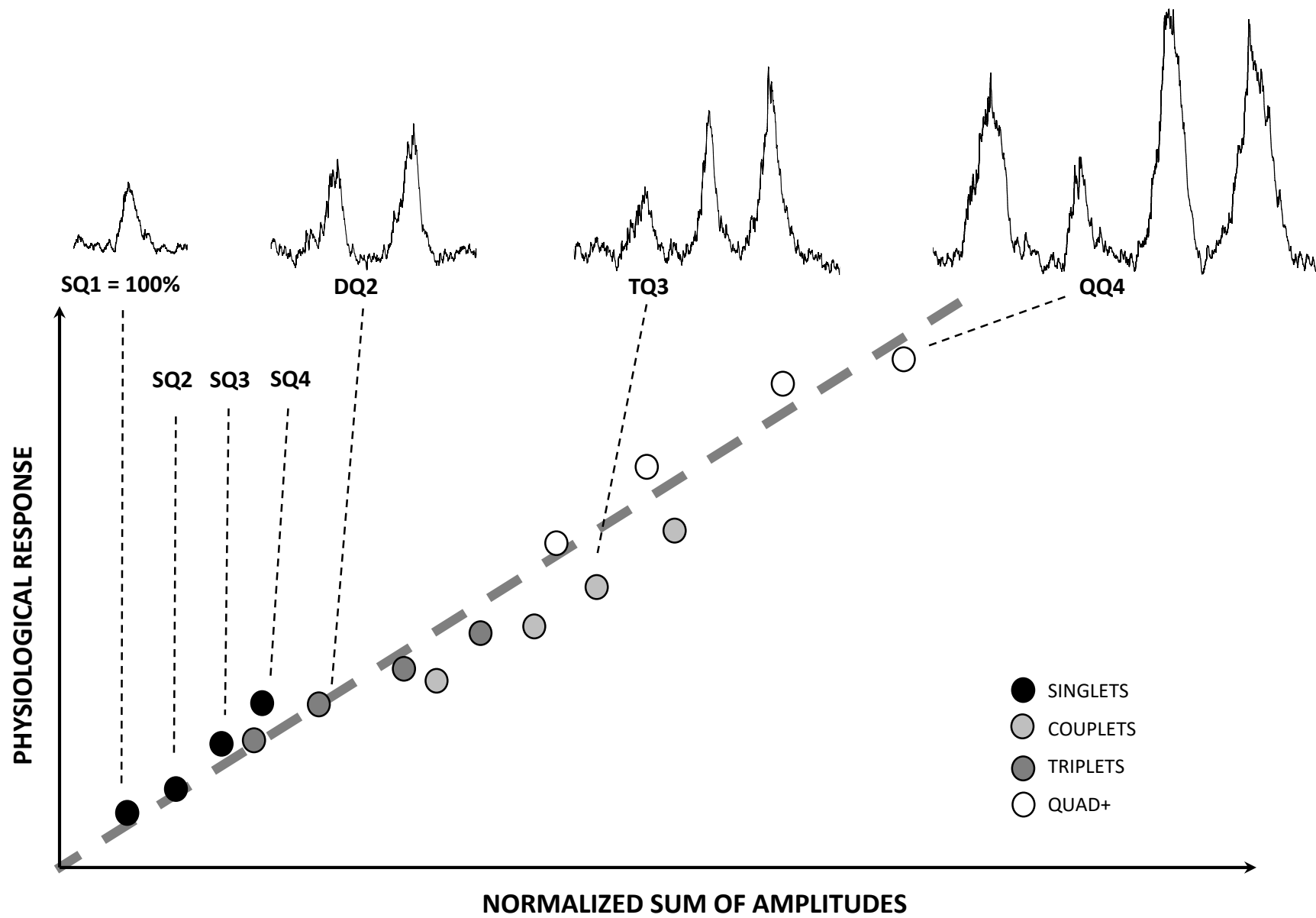
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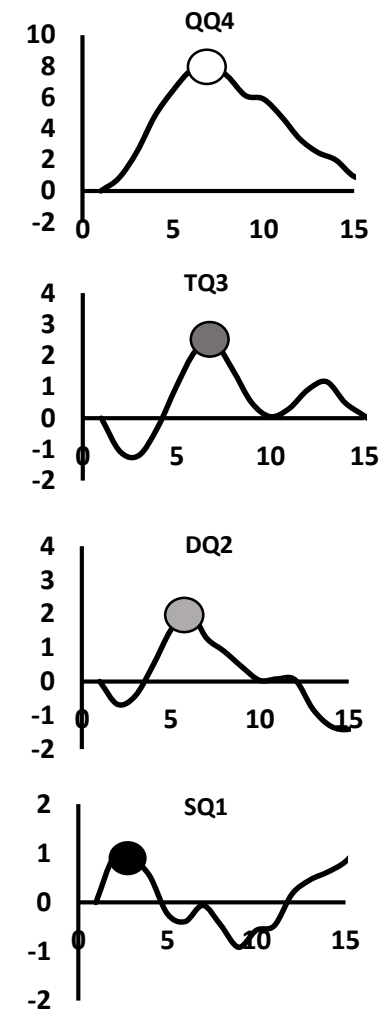
**Table 1:** Participant demographics and physiological characteristics

	LOW ALTITUDE NATIVES		HIGH ALTITUDE NATIVES		Main Effect of Group	Paired Ttest (Low to High)
	Low Altitude (344m)	High Altitude (5050m)	Tibetan Sherpa (5050m)	Andean (4380m)		
	(n= 14; 12 M)	(n= 14; 12 M)	(n= 8; 8 M)	(n= 15; 15 M)		
				p value	p value	
Age (yrs)	27 ± 1	27 ± 1	32 ± 5	42 ± 3	<b>0.001</b>	-
Height (cm)	177 ± 2	177 ± 2	168 ± 3	161 ± 1	<b>&lt; 0.001</b>	-
Weight (kg)	72 ± 3	69 ± 2	64 ± 4	70 ± 3	0.396	-
BMI (kg/m <sup>2</sup> )	23 ± 1	22 ± 1	23 ± 1	27 ± 1	<b>0.002</b>	-
Heart Rate (bpm)	53 ± 3	64 ± 4	68 ± 5	68 ± 3	0.625	<b>0.03</b>
R-R Interval (sec)	1.2 ± 0.10	0.97 ± 0.05	0.93 ± 0.11	0.9 ± 0.04	0.655	<b>0.025</b>
Mean Arterial Pressure (mmHg)	84 ± 2	86 ± 3	83 ± 3	86 ± 2	0.773	0.638
MAP Delta Mean (mmHg)	1.1 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	0.87 ± 0.1	<b>0.009</b>	0.26
Systolic Arterial Pressure (mmHg)	118 ± 3	112 ± 3	110 ± 3	110 ± 2	0.871	0.072
Diastolic Arterial Pressure (mmHg)	67 ± 2	70 ± 3	65 ± 3	72 ± 1	0.154	0.146
Cardiac Output (L/min)	5.3 ± 0.3	5.3 ± 0.3	6 ± 0.6	6 ± 0.3	0.441	1
Total Peripheral Resistance (mmHg/L/min)	17 ± 1	17 ± 1	16 ± 2	15 ± 1	0.463	0.595
Total Peripheral Conductance (L/mmHg/min)	0.063 ± 0.003	0.063 ±	0.07 ± 0.01	0.068 ± 0.004	0.218	0.612
Peripheral Oxygen Saturation (%)	-	82 ± 1	82 ± 1	81 ± 1	0.595	-
Burst Incidence (bursts/100 heart beats)	22 ± 3	47 ± 4	30 ± 5	57 ± 4	<b>0.002</b>	<b>&lt; 0.001</b>
Burst Frequency (bursts/min)	11 ± 1	30 ± 2	23 ± 4	39 ± 3	<b>0.006</b>	<b>&lt; 0.001</b>

BMI, Body Mass Index; Cardiac output, total peripheral resistance and total peripheral conductance calculated from finger photoplethysmography. One-way ANOVA used to determine differences between high altitude groups; paired, two tailed t-tests used to compare lowlanders from low to high altitude. Values are mean +/- SE.

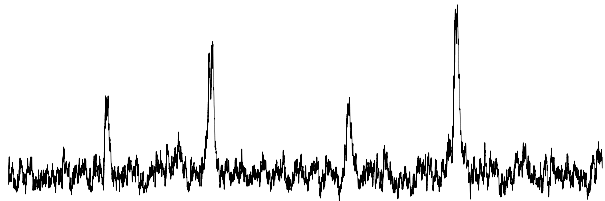


### Associated Peak Physiological Responses



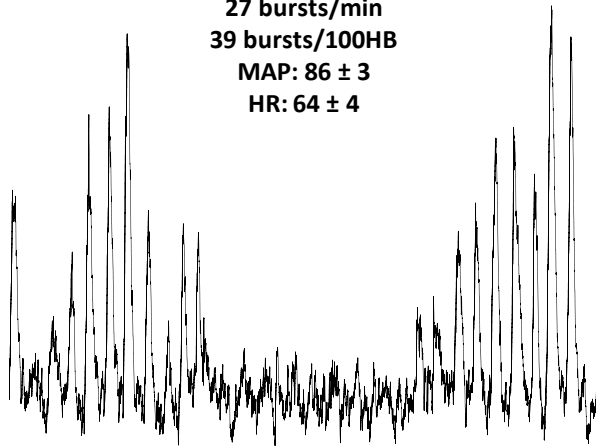
**A** Lowlanders LA (344m)

8 bursts/min  
21 bursts/100HB  
MAP:  $84 \pm 2$   
HR:  $53 \pm 3$



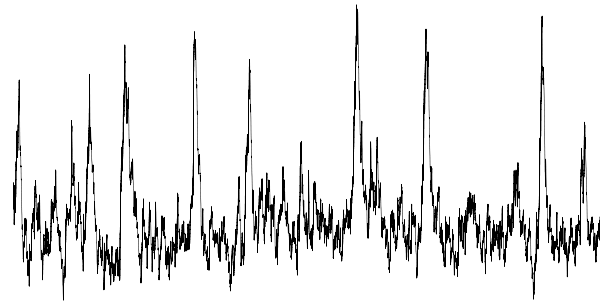
**B** Lowlanders HA (5050m)

27 bursts/min  
39 bursts/100HB  
MAP:  $86 \pm 3$   
HR:  $64 \pm 4$



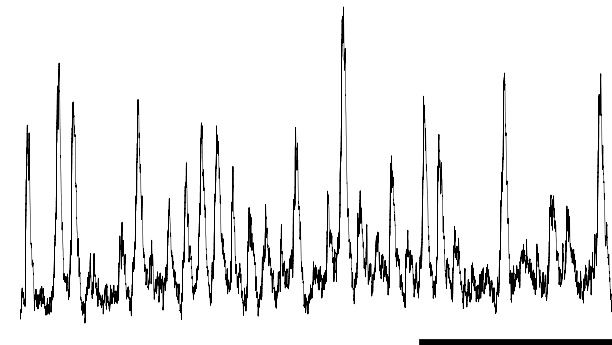
**C** Sherpa HA (5050m)

19 bursts/min  
28 bursts/100HB  
MAP:  $83 \pm 3$   
HR:  $68 \pm 5$



**D** Andeans HA (4300m)

47 bursts/min  
60 bursts/100HB  
MAP:  $86 \pm 2$   
HR:  $68 \pm 3$



10 sec

