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±0.0060 vs low-altitude, 0.0134±0.080; p=0.03). Transduction was elevated in Sherpa

80 (MAP slope, 0.012±0.007) compared to Andeans (0.003±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

INTRODUCTION:

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

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

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±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)

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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 (200µm diameter, 35 mm long, tapered to a 1-5 µm 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   satruation, and other cardiovascular metrics were extracted on a beat-by-beat basis for each

205   individual over 11 ± 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 (α') value

255   corrected for multiple comparisons (c). This was performed by adjusting the a priori alpha (α,

256   0.05) using the experiment-wise error rate (α_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 ± standard deviation (SD) unless otherwise indicated.   All statistical

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 (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±2 vs 89±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±14 vs 37±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 ±1.1

299   vs 0.83 ±0.58 mmHg; $p<0.001$) and couplet (4.2±2.0 vs 1.8±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 ± 0.00014; high altitude, 0.00007 ± 0.00008;

312    $p=0.032$).　The transduction slope for MAP was blunted at high altitude (MAP slope,

313   0.0075±0.0060 at high altitude versus 0.0134 ±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 ± 0.007) and R-R interval

337   compared to Andeans (MAP, 0.0031 ± 0.0024; R-R Interval, 0.00003 ± 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 ($r=0.578$;

12

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 ± 1.9s

352 following burst sequences; changes in R-R Interval occurred 2.1 ± 1.0s following bursts;

353 changes in CO occurred 2.4 ± 1.0s 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 ± 2s) also followed peak

356 changes in both R-R Interval (1.9 ± 1.1s) and CO (2.9 ± 1.1s) (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 ±

359 2.5s) followed peak changes in both CO (2.4 ± 1.3s) and R-R interval (2.1 ± 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 ± 2.5s) also followed peak changes in CO (1.8 ± 1.0s) and R-R interval (1.3 ± 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 be 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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588

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730

731

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 ± 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 ± 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+,

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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 ± 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

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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Table 1: Participant demographics and physiological characteristics

	LOW ALTITUDE NATIVES		HIGH ALTITUDE NATIVES			
	Low Altitude (344m) (n= 14; 12 M)	**High Altitude (5050m)** (n= 14; 12 M)	**Tibetan Sherpa (5050m)** (n= 8; 8 M)	**Andean (4380m)** (n= 15; 15 M)	**Main Effect of Group** p value	**Paired Ttest (Low to High)** p value
Age (yrs)	27 ± 1	27 ± 1	32 ± 5	42 ± 3	**0.001**	-
Height (cm)	177 ± 2	177 ± 2	168 ± 3	161 ± 1	**< 0.001**	-
Weight (kg)	72 ± 3	69 ± 2	64 ± 4	70 ± 3	0.396	-
BMI (kg/m²)	23 ± 1	22 ± 1	23 ± 1	27 ± 1	**0.002**	-
Heart Rate (bpm)	53 ± 3	64 ± 4	68 ± 5	68 ± 3	0.625	**0.03**
R-R Interval (sec)	1.2 ± 0.10	0.97 ± 0.05	0.93 ± 0.11	0.9 ± 0.04	0.655	**0.025**
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	**0.009**	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 ± 0.003	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	**0.002**	**< 0.001**
Burst Frequency (bursts/min)	11 ± 1	30 ± 2	23 ± 4	39 ± 3	**0.006**	**< 0.001**

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.
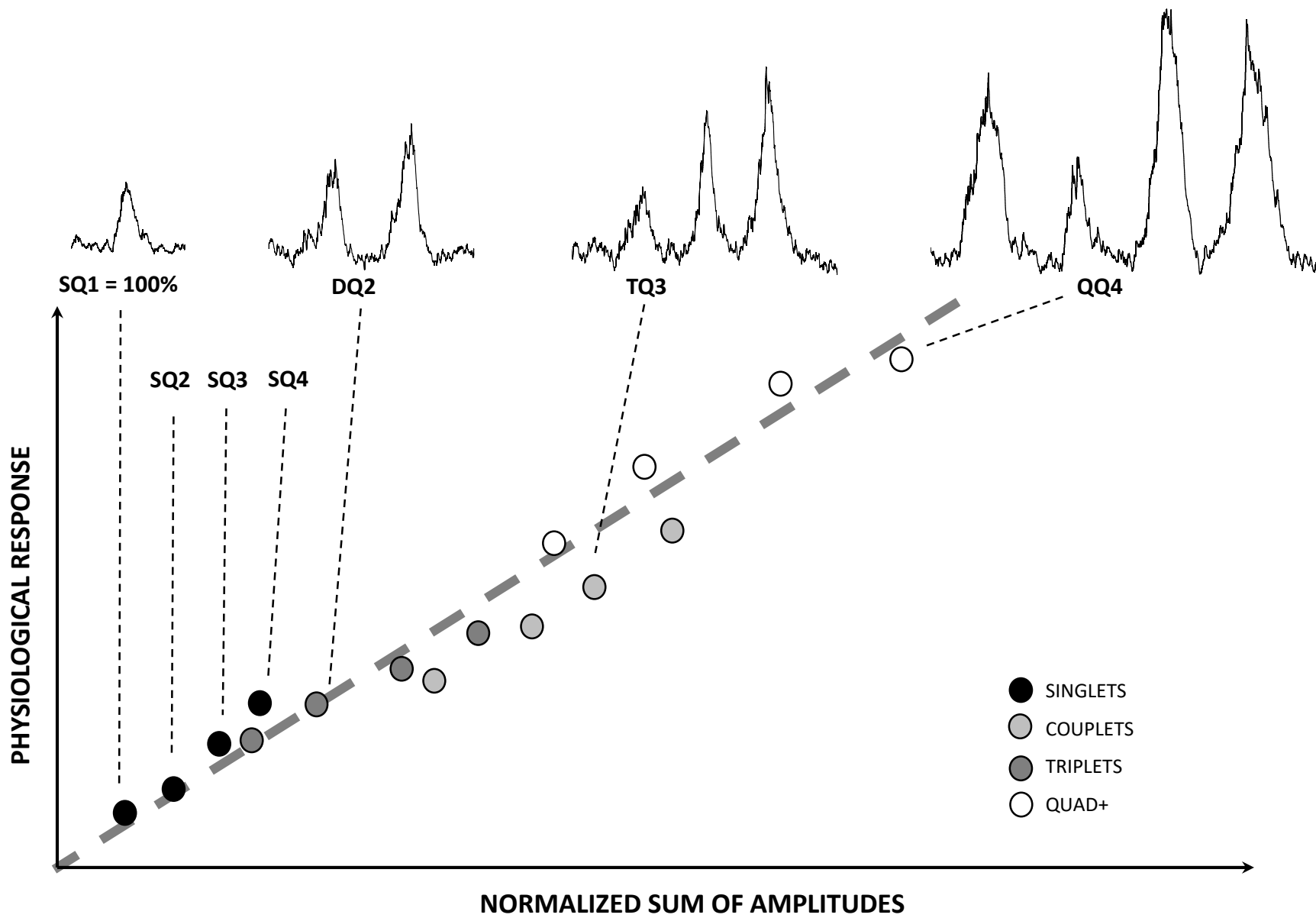
Associated Peak Physiological Responses

QQ4

TQ3

DQ2

SQ1

SQ1 = 100%

DQ2

TQ3

QQ4

SQ2   SQ3   SQ4

PHYSIOLOGICAL RESPONSE

NORMALIZED SUM OF AMPLITUDES

SINGLETS
COUPLETS
TRIPLETS
QUAD+
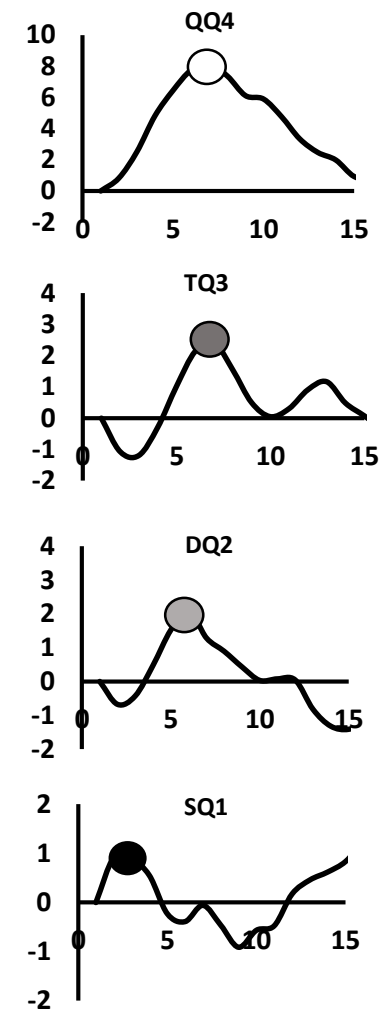
A Lowlanders LA (344m)
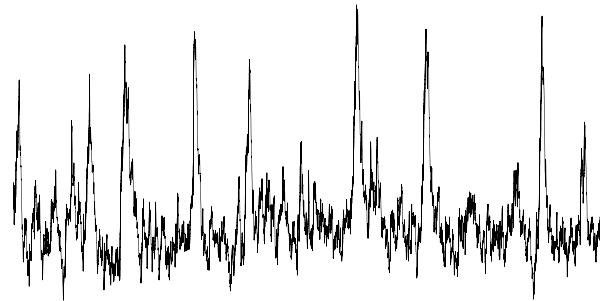
8 bursts/min
21 bursts/100HB
MAP: 84 ± 2
HR: 53 ± 3
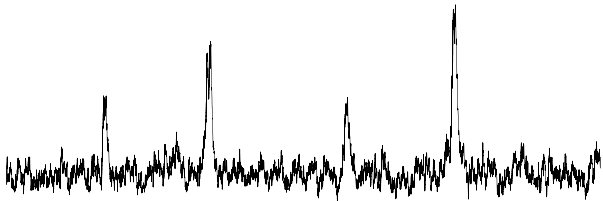
B Lowlanders HA (5050m)
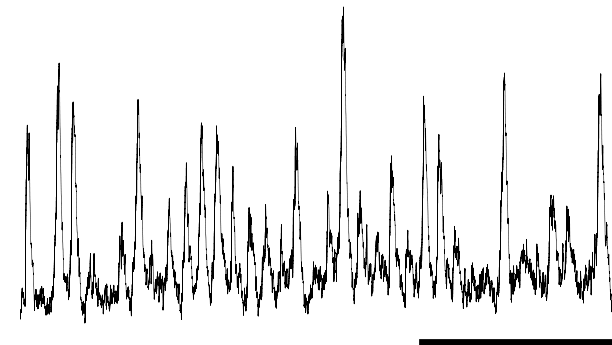
27 bursts/min
39 bursts/100HB
MAP: 86 ± 3
HR: 64 ± 4
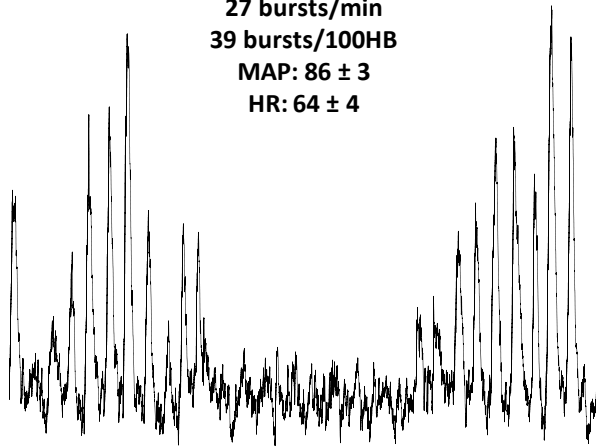
C Sherpa HA (5050m)
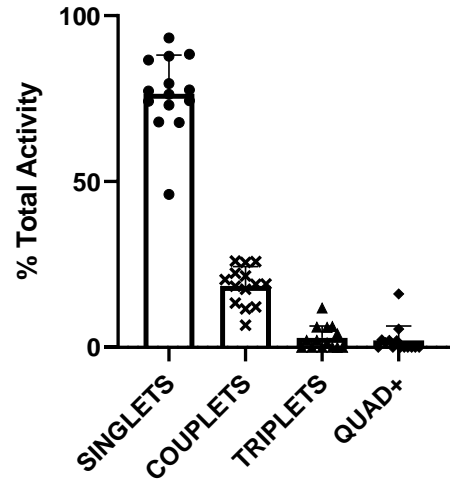
19 bursts/min
28 bursts/100HB
MAP: 83 ± 3
HR: 68 ± 5

D Andeans HA (4300m)

47 bursts/min
60 bursts/100HB
MAP: 86 ± 2
HR: 68 ± 3

10 sec

LL LA   LL HA   SHERPA   ANDEANS

A

Change in MAP (mmHg)

B

Change in MAP (mmHg)

- ● SINGLETS
- ✕ COUPLETS
- ▲ TRIPLETS
- ■ QUAD+

A

| | LL LA | LL HA | SHERPA | ANDEANS |

Change in R-R Interval (s)
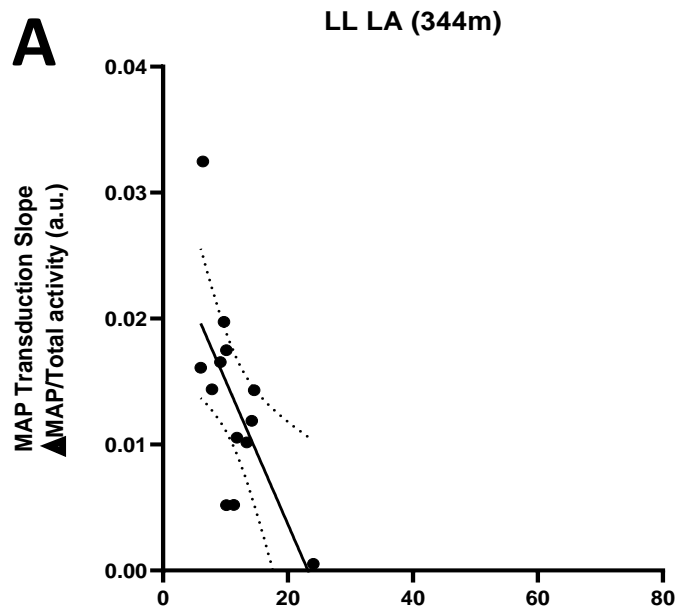
B

Change in R-R Interval (s)

● SINGLETS
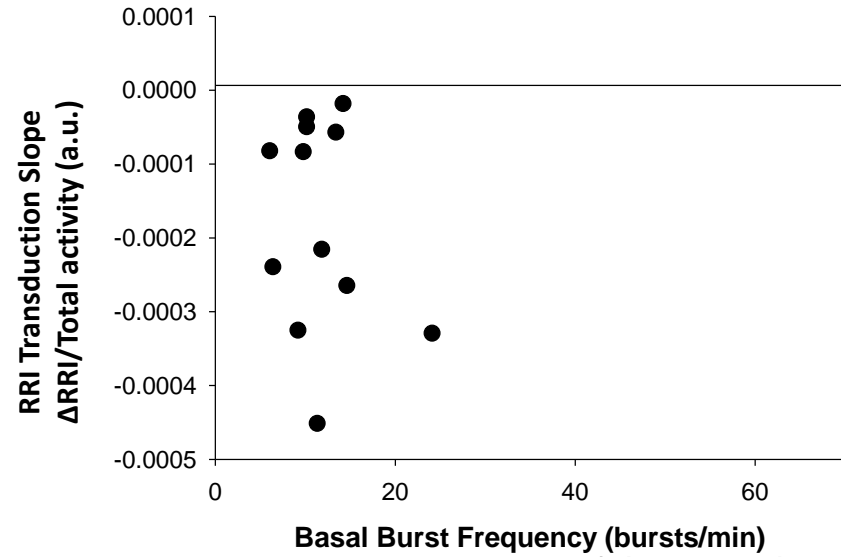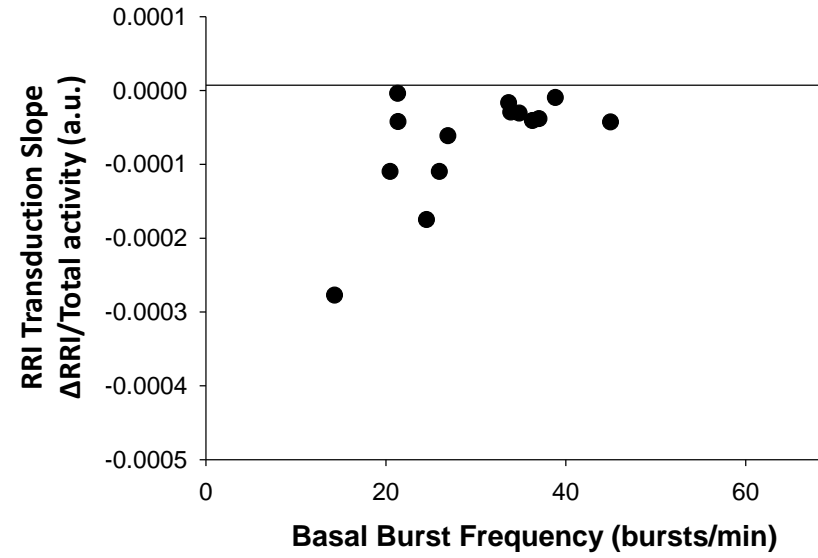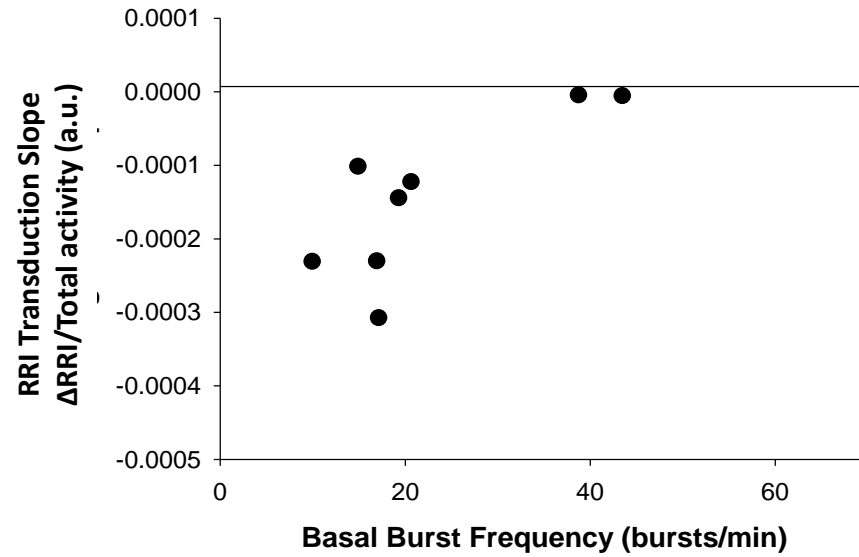✕ COUPLETS
▲ TRIPLETS
■ QUAD+
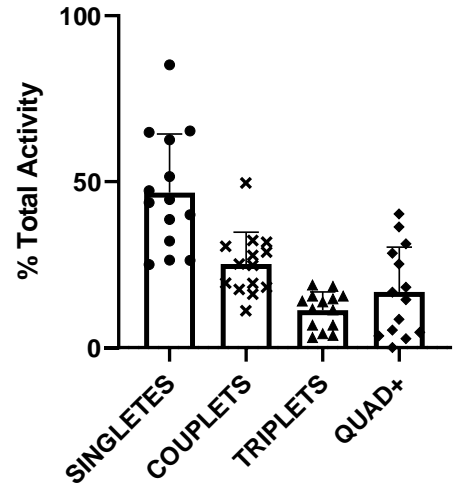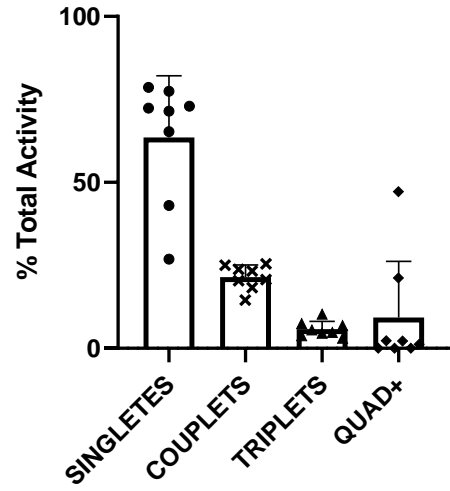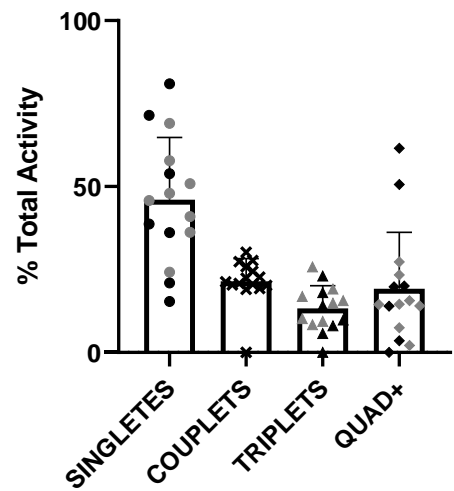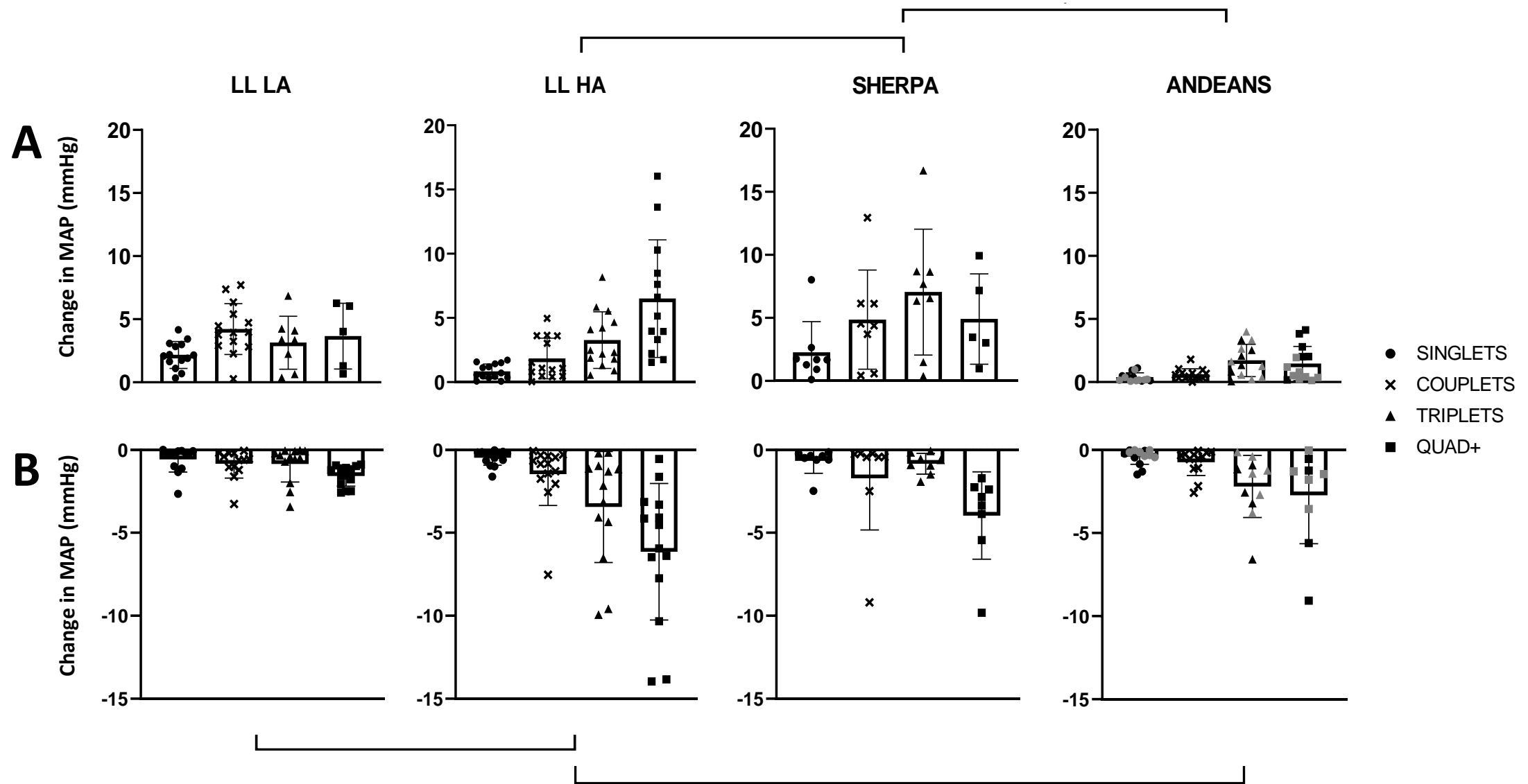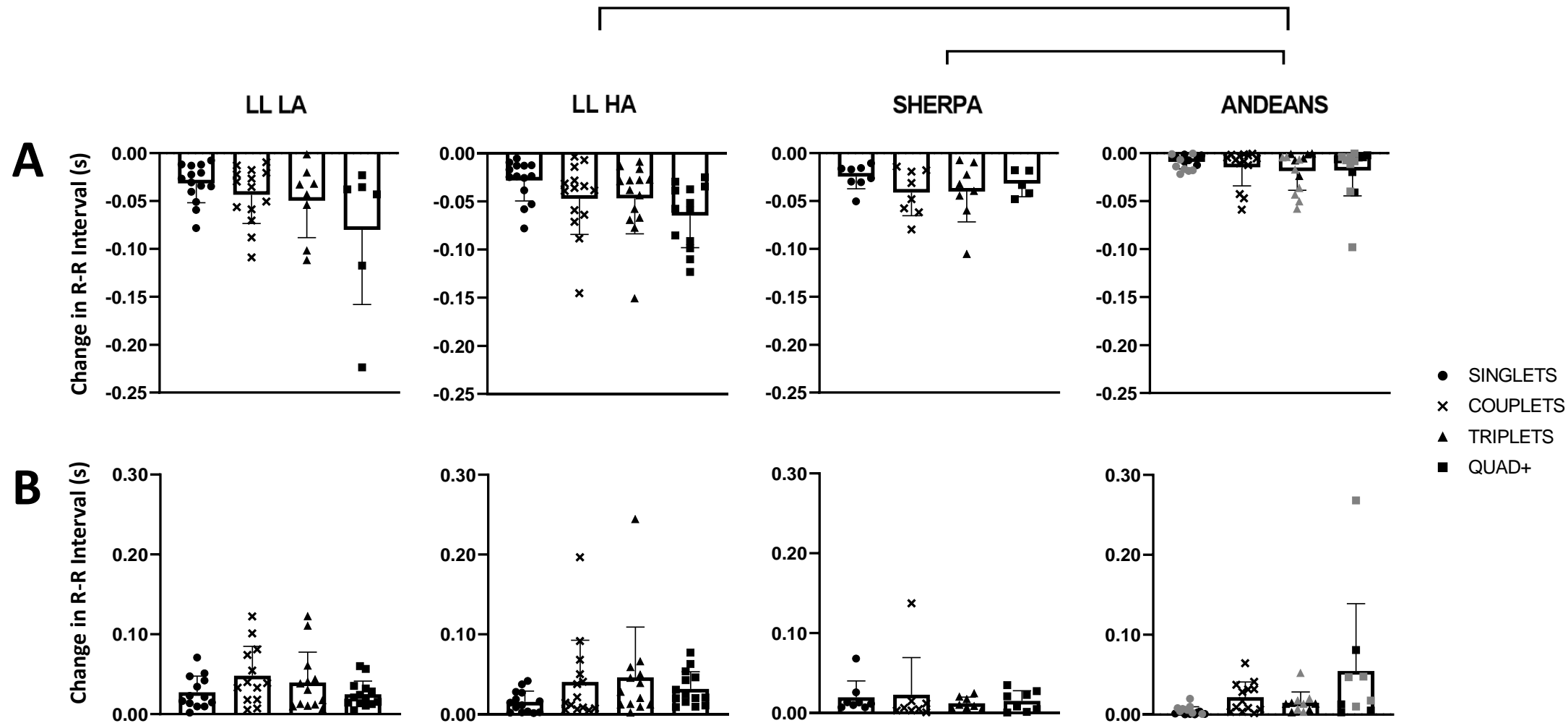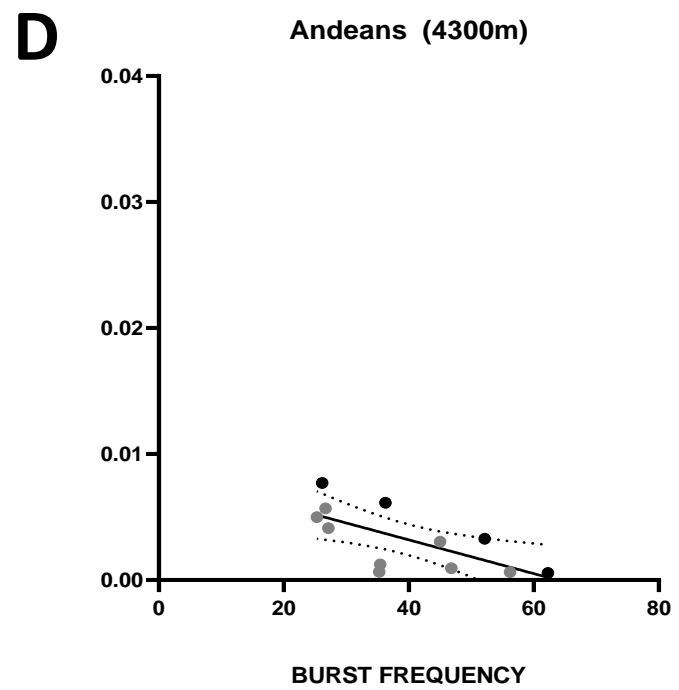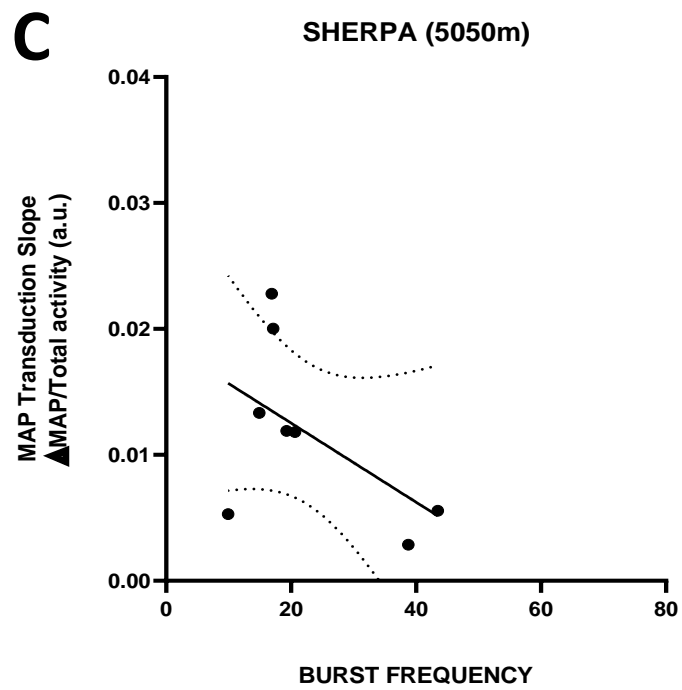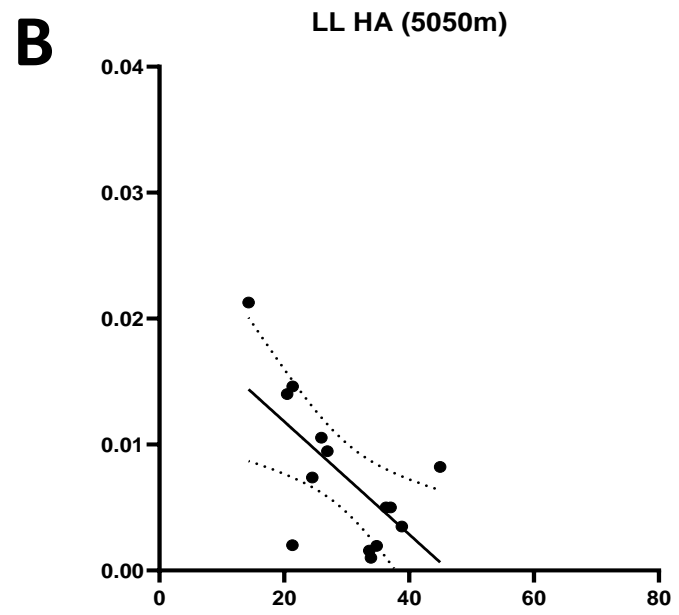
A LL LA (344m)

B LL HA (5050m)

C SHERPA (5050m)

D ANDEANS (4300m)

All panels — x-axis: Basal Burst Frequency (bursts/min); y-axis: RRI Transduction Slope ΔRRI/Total activity (a.u.)