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# Influence of recent altitude exposure on sea level sympathetic neural & hemodynamic responses to orthostasis

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ABSTRACT

Although it has been shown that muscle sympathetic nerve activity increases during high altitude exposure, mechanisms of sympathoexcitation and blood pressure control after return from altitude are not well described. We hypothesized that: (1) living for 12 days at 4300 m (Pikes Peak, Colorado) would result in increased muscle sympathetic nerve activity 24 h after return to sea level; (2) post-Pikes Peak sympathetic neural and hemodynamic responses to orthostasis would be decreased due to a potential 'ceiling effect' on sympathetic activity; and (3) the magnitude of individual increases in sympathetic nerve activity post-Pikes Peak would be inversely related to baseline sympathetic nerve activity before traveling to altitude. Muscle sympathetic nerve activity, heart rate and blood pressure were measured in 9 healthy individuals (24 ± 8 years) in supine, 30° and 45° head-up tilt positions. Measurements were conducted twice at sea level, once before (pre-Pikes Peak) a 12 day residence at 4300 m, and once within 24 h of return (post-Pikes Peak). Supine muscle sympathetic nerve activity was higher (post: 27 ± 5 vs pre: 17 ± 6 bursts/min) upon return from altitude ($p < 0.05$). Individual values for pre-Pikes Peak sympathetic activity were inversely related to post-altitude sympathoexcitation ($r = -0.69$, $p < 0.05$). There were no differences in neural or cardiovascular responses to tilt between pre and post- Pikes Peak ($p > 0.05$). We conclude that 12 days' residence at 4300 m causes a sustained sympathoexcitation which does not impair the ability of muscle sympathetic nerves to respond appropriately to orthostasis.

## 1. Introduction

Acute exposure to high altitude alters several aspects of cardiovascular regulation, including increased muscle sympathetic nerve activity (Hansen and Sander, 2003) and (paradoxically) increased potential for both orthostatic intolerance (Halliwill and Minson, 2002; Fulco et al., 1985) and hypertension (Wolfel et al., 1994; Ledderhos et al., 2002). Whether these aspects of dysfunction continue in the days following return to sea level is unclear, but has significant relevance to both clinical and recreational populations. Our goal in the present study was to investigate muscle sympathetic neural responses during the time period immediately after a 12 day sojourn to 4300 m altitude.

The "adaptive" aspect of the chemoreflex-mediated sympathoexcitation during hypoxic exposure is that an increase in perfusion pressure, and therefore blood flow, may maintain oxygen delivery to a given tissue or organ system under conditions of decreased partial pressure of inspired $O_2$. However, this sympathoexcitation can also have maladaptive consequences, such as increased blood pressure (Wolfel et al., 1994; Ledderhos et al., 2002). Furthermore, augmented altitude-induced sympathoexcitation has been shown to be associated with development of high-altitude pulmonary edema (HAPE) (Duplain et al., 1999).

Hansen and Sander (2003) showed that sympathoexcitation associated with prolonged very high altitude exposure (4 weeks at 5260 m, Bolivian Andes) persisted into the 3rd day following return to sea level (SL). With this information in mind, we designed the present study to evaluate novel aspects and implications of the sympathoexcitation after return from altitude, by addressing 3 major goals. First, we measured muscle sympathetic nerve activity (MSNA) after a shorter exposure to a more moderate altitude (12 days at Pikes Peak [PP], Colorado, 4300 m). Second, we assessed whether the immediate post-altitude period was associated with altered neural and hemodynamic responses to orthostasis (head-up tilt) after return to SL. Third, we evaluated whether inter-individual variability in pre-altitude resting MSNA was

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associated with individual levels of sympathoexcitation (delta MSNA) after altitude exposure.

We hypothesized that 12 days at 4300 m altitude would result in sympathoexcitation (increased resting MSNA) which would persist into the first 24 h after return to SL. Because there is a limit to the extent to which MSNA can increase, we hypothesized that altitude-mediated sympathoexcitation would result in decreased responses to orthostasis via a "ceiling effect". Finally, we hypothesized that individuals with higher pre-PP MSNA would have smaller changes in MSNA post-PP. We tested these hypotheses by directly measuring MSNA and systemic hemodynamics during supine rest and in response to passive head-up tilt in young, healthy men and women before and within 24 h of return from a 12-day sojourn at 4300 m.

## 2. Methods

### 2.1. Ethical approval

Nine healthy, non-smoking individuals (7 M, 2 F; age: 24 ± 8 years, height: 181 ± 10 cm, Pre-altitude weight: 76 ± 12 kg; Post-altitude weight: 74 ± 12 kg) volunteered to participate in this study. The neural and hemodynamic measurements for the present manuscript were conducted as a subset of a larger study about altitude acclimatization, from which other data have already been published (Beidleman et al., 2017). The study was approved by the Institutional Review Board of the US Army Research Institute of Environmental Medicine (USARIEM). All volunteers provided written and verbal acknowledgment of their informed consent and were made aware of their right to withdraw without prejudice at any time. Investigators adhered to the Department of Defense policies for protection of human subjects (DoD Instruction 3216.02) and the research was conducted in accordance with 32 CFR Part 219. All 9 volunteers were unacclimatized, healthy men and women, non-smokers, physically active, with normal pulmonary function (assessed at SL). Participants were asked to abstain from alcohol consumption for 24 h prior to testing, and both female participants had a negative serum pregnancy test within 72 h before testing. Neither of the two women subjects was taking oral contraceptives. We did not control for menstrual cycle, but did ask for information about menstrual cycle phase. One subject was in the early follicular phase during her pre-PP trial, and late luteal phase during her post-PP trial. The other was in the early luteal phase during her pre-PP trial and early follicular during her post-PP trial.

### 2.2. Timeline and experimental protocol

Participants reported to the USARIEM laboratory at SL (50 m) on two occasions, once 2–3 weeks prior to (pre-PP), and once within 24 h after (post-PP), a 12-day sojourn to the U.S. Army Pikes Peak Laboratory Facility, Colorado (4300 m).

Details of the PP exposure are described in detail by Beidleman et al. (2017). Briefly, subjects were driven to the summit of PP (4300 m), where they resided under comfortable ambient and living conditions for 12 days. Within 24 h of return from PP, all post-PP measurements for each subject were performed in the same order, and at approximately the same time of day as during the pre-PP baseline measurements. While at PP, participants maintained aerobic fitness by participating in daily hikes and/or treadmill exercise; daily energy expenditure was, on average, approximately 3000 kcal/day. During their stay at PP, they ate ad libitum from a wide variety of offered foods; diet was not specifically controlled.

On both test days, subjects were well hydrated and ate a small breakfast prior to reporting to the laboratory. Subjects reported to a temperature-controlled laboratory (22–24 °C) and rested supine during instrumentation for 3-lead electrocardiogram (ECG) and blood pressure (BP). Subjects were then instrumented for measurement of muscle sympathetic nerve activity (MSNA) in the peroneal nerve. Once a good nerve signal was found, 7 min of supine baseline data were recorded, followed by 2 min each of 30° head up tilt (HUT) and 45° HUT while the participant rested quietly. All subjects had MSNA recorded in the right peroneal nerve on both occasions; care was taken to ensure that at least 4 weeks had elapsed between the pre-PP and post-PP measurements.

### 2.3. Measurements

Heart rate (HR) was recorded continuously from the ECG. Beat-by-beat arterial pressure was measured via finger photoplethysmography (Finometer, Finapres Medical Systems, Netherlands) and absolute values were verified by periodic measurements using an automated upper arm sphygmomanometer (Cardiocap, Datex Ohmeda, Madison, WI).

MSNA was recorded via peroneal microneurography using a tungsten microelectrode according to the procedures detailed by Sundlöf and Wallin (1977). Briefly, the microelectrode was placed percutaneously and manipulated using fine movements until a muscle sympathetic fascicle was identified when taps on the muscle belly or passive muscle stretch evoked mechanoreceptive impulses. Muscle nerve activity was confirmed when no afferent neural response was evoked by skin stimuli. The signal was amplified 80,000-fold, band-pass filtered (700 to 2000 Hz), rectified and integrated (resistance-capacitance integrator circuit, time constant 0.1 s) by a nerve-traffic analyzer.

### 2.4. Data analysis

MSNA, ECG and BP data were sampled at 250 Hz using WinDaq hardware and software (WinDaq, DATAQ Instruments, Akron, OH, USA) and stored for offline analysis. MSNA, HR, systolic (SBP) and diastolic blood pressure (DBP) are reported as the average of the last 5 min of the supine period and of each 2 min period of HUT. Sympathetic bursts were identified and quantified by an experienced investigator (NC), using Windaq software. Sympathetic activity was identified if bursts were pulse-synchronous, demonstrated a characteristic shape with ~1.3-sec latency from the previous R wave, and had at least a 3:1 signal-to-noise ratio. MSNA was expressed as burst frequency (BF; bursts/min) and burst incidence (BI; bursts/100 heartbeats).

To attempt to avoid confusion regarding changes (Δ values) for MSNA, we defined the following: changes in supine MSNA associated with altitude exposure are referred to as PPΔMSNA (= post-PP MSNA − pre-PP MSNA). Changes in MSNA associated with orthostasis (both pre- and post-PP) are referred to as HUTΔMSNA (= HUT MSNA − supine MSNA).

### 2.5. Statistics

Group data are expressed as mean ± SD. Linear regression analyses and *t*-tests were used to determine the relationships between pre-PP and post-PP for systemic hemodynamics (HR, SBP & DBP) and MSNA. A two-way, repeated measures ANOVA was used to compare data across test days and postures. A Holm-Sidak post-hoc test was used when significant main effects were found. $p < 0.05$ was accepted as statistically significant.

## 3. Results

### 3.1. Systemic hemodynamics

Table 1 shows values for HR, SBP, and DBP during pre- and post-PP. No significant differences were seen in HR or BP between pre- and post-PP during baseline, 30°, or 45° HUT. As expected, HR increased significantly from supine to 30° HUT, and from supine to 45° HUT during both pre- and post-PP ($p < 0.05$). HR was significantly higher at 45° HUT compared to 30° HUT at both time points ($p < 0.05$). SBP decreased significantly between supine and 30° HUT, and supine and 45° HUT both during pre- and post-PP ($p < 0.05$). No differences existed