AltitudeOmics: Effect of Hypoxia and Hyperoxia on Baroreflex Sensitivity

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Abstract

This paper is part of a series titled "AltitudeOmics" that together represent a group of studies that explore the basic mechanisms controlling human acclimatization to hypoxia. This study aims at analyzing the baroreflex sensitivity (BRS) at sea level, in acute and chronic hypoxia and test whether hyperoxia reverts the hypoxic effects. Twenty-one young, healthy subjects underwent experimental trials near sea level, and two times at high altitude. BRS was calculated using the sequence method, spectral method, transfer function and the standard deviation method. Results showed a decrease in BRS with hypoxic exposures. Hyperoxia reverted the hypoxic effects in acute hypoxia only. In chronic hypoxia, BRS reset to lower values but behaved comparably to normoxia.

1. Introduction

Baroreflex sensitivity (BRS) is a marker of the autonomic control of the cardiovascular system. As one of the two main markers of autonomic nervous system, alongside heart rate variability (HRV), BRS has been shown to provide valuable information for cardiovascular diseases such as congestive heart failure and coronary artery disease [1] [2]. In addition, physiological, such as age and gender [3] [4] [5] and non-physiological factors such as exercise have been shown to influence BRS [1] [6].

Baroreflex is a vital homeostatic mechanism which maintains nearly constant levels of blood pressure in the systemic circulation, yet it has rarely been studied during acclimation at very high altitude in humans. We hypothesized that very high altitude (~5,000m) where ambient oxygen pressure is about half of that at sea level (SL) would be a very destabilizing stimulus for baroreflex sensitivity (BRS). Arterial oxygen content is severely decreased in acute hypoxia and progressively increases with acclimatization, which contributes to the successful acclimation occurring in the great majority of people exposed to chronic hypoxia. As such, we hypothesized that BRS would also contribute to the successful acclimation by adjusting its level during the acclimation process. The aim of this work is to assess BRS at rest in acute and chronic hypoxia and determine whether a hyperoxic stimulus reverses the effects of hypoxic exposures.

2. Methods

2.1. Ethical approval

This study was conducted as part of the AltitudeOmics project. Institutional ethics approval was obtained from the Universities of Colorado and Oregon and the U.S. Department of Defense Human Research Protection Office. This study follows the Declaration of Helsinki. After being informed of the procedures of this study, all participants gave written informed consent prior to participation.

2.2. Study design

Young, healthy sea level (SL) residents were recruited from the greater Eugene, Oregon, area (elevation 128 m) and screened to exclude anyone who was born or had lived at altitudes >1,500 m for more than 1 year or had traveled to altitudes >1,000 m in the past 3 months. SL measurements occurred in Eugene. Approximately 4 weeks following SL measurements, subjects were flown to La Paz, Bolivia. They breathed supplemental oxygen during the drive to the Chacaltatya research station at 5,260 m. Acute responses to high altitude were assessed between

2 to 4 h after arrival and cessation of supplemental oxygen (ALT1). Subjects then acclimatized at 5,260 m over the next 15 days. On the 16th day (ALT16), measurements were repeated at 5,260.

This report focuses on novel data and novel analysis regarding BRS during acute and chronic hypoxic and hyperoxic exposures. The entire experimental protocol of the AltitudeOmics project is available in details elsewhere [7]. We have carefully avoided replication of data among reports, except for basic anthropometric data [e.g., age, height, weight].

2.3. Subjects

We studied 21 subjects (twelve men and nine women) at SL, ALT1 and ALT16, aged 21 ± 1 years old, height 175.8 ± 7.9 cm, weight 69.7 ± 9.0 kg, BMI 22.4 ± 1.8 kg/m^2.

2.3. Measurements

All subjects were familiarized with study procedures at least 48 h prior to SL data recording. Subjects followed standardized exercise and dietary regimens for 24 h before each measurement period. At SL, ALT1 and ALT16, a 22-gauge catheter was inserted into a radial artery at least 1 h before instrumentation. Arterial blood pressure (ABP) was monitored via a fluid-filled pressure transducer (Deltran II; Utah Medical Products, Midvale, UT) attached to the radial artery catheter.

Continuous analog data for ABP were recorded at 200 Hz (PowerLab 16/30; ADInstruments) and directly stored on a dedicated computer for offline analysis.

2.4. Protocol

After the subjects were instrumented, they underwent a 10-min period, comfortably seated on a chair, in upright position, breathing room air. Immediately after, the subjects breathed a hyperoxic mixture for 6 min adjusted so that end tidal O_2 pressure ($PetO_2$) ~250 mmHg and end tidal CO_2 pressure ($PetCO_2$) was clamped at 40 mmHg.

2.5. Data processing

2.5.1. Extraction of heartbeats

Heartbeats were extracted directly from the ABP recordings. Initially, systolic blood pressure (SBP) was extracted from the ABP waveform with heartbeats representing the time of their occurrence. However, low sampling rates (< 250 Hz) may produce jitter in the estimation of peaks [8] [9]. For instance, at 200 Hz the highest time resolution is within a confidence interval of five ms. In order to refine the location of heartbeats and the SBP values, a second order polynomial was interpolated for each extracted peak using four neighbor samples from the ABP waveform (two immediately before and two immediately after). Heartbeats were selected as the location maximum of the interpolated polynomial. Furthermore, SBP values were updated as the maximum in their corresponding polynomial. Finally, the inter-beat intervals (IBI) were created as the interval between successive peaks.

2.5.2. Measuring baroreflex sensitivity

For this study, BRS was calculated using the sequence [10], spectral [11], transfer function [12], and the standard deviation methods [13].

Sequence Method (BRS-Seq): This index of BRS is based on the identification of at least three consecutive beats in which strict increase (decrease) in SBP are followed by strict increase (decrease) in the IBI [10]. Fixed minimal changes thresholds were considered for BP and IBI to validate a sequence. More specifically, a minimum change of 1 mmHg between two consecutive SBP values and five milliseconds were considered for IBI, as the lower threshold for increase (decrease) sequence. Furthermore, correlation coefficient between changes in SBP and IBI to validate a sequence was 0.85. Finally, a minimum number of five sequences was set to validate a BRS estimate.
For each SBP-IBI trend, the slope of the regression line between changes in SBP and IBI was calculated, and BRS was obtained as the average of all slopes.

Spectral Method (BRS-LF, BRS-HF): This measure of BRS works based on the concept that spontaneous oscillation in SBP prompts oscillation in IBI, at the same frequency [11]. In this method, BRS is calculated as the square root of the ratio of the autoregressive spectral power between IBI and SBP. In this measure, spectral BRS was calculated in the low-frequency band (0.04-0.15) Hz, and the high-frequency band (0.15-0.4) Hz, when coherence between the SBP and IBI spectral components was greater than 0.5.

Transfer Function Method (BRS-TF): Another method to measure the BRS is the transfer function method. This method calculates BRS by averaging the transfer function value between SBP and IBI in the frequency range of [0.07-0.14] Hz [12].

Standard Deviation Method (BRS-SD): This simple method calculates BRS as the standard deviation of IBI divided by that of the SBP [13].

3. Results

3.1. Baroreflex sensitivity data

Baroreflex sensitivity was measured for the twenty-one

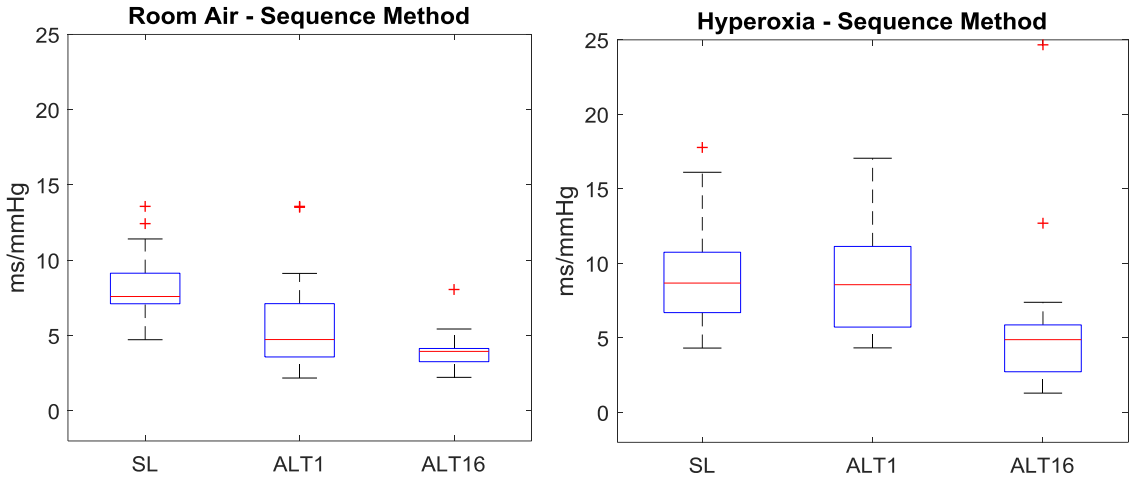

Figure 1- Boxplot of BRS in different altitude in room air and hyperoxic conditions, sequence method.

subjects at SL, ALT1, and ALT16, separately for the ambient air and the hyperoxic conditions. Detailed BRS measurements are reported in Table 1. The boxplot of the BRS at each altitude and for each setting, i.e. room air and hyperoxia, is illustrated in Fig. 1. This figure shows the evolution of the BRS for the sequence method. The changes in the standard deviation, transfer function, and the spectral methods were consistent with that of the sequence method.

Table 1- Baroreflex Sensitivity Data.

Parameter /State	SL (mean±std)	ALT1 (mean±std)	ALT16 (mean±std)
Room air (ms/mmHg)			
BRS-Seq	8.30±2.27	5.97±3.42	4.04±1.31
BRS-LF	11.12 ±3.21	9.18±7.92	6.49±2.21
BRS-HF	8.78±3.58	5.58±2.98	3.65±0.92
BRS-TF	9.45±2.66	6.41±4.43	5.34±1.87
BRS-SD	9.72±2.69	7.96±6.53	5.69±1.92
Hyperoxia (ms/mmHg)			
BRS-Seq	9.18±3.45	11.21±10.19	5.78±5.42
BRS-LF	12.83±5.84	15.77±12.40	9.12±9.51
BRS-HF	9.84±4.30	15.19±16.59	8.45±14.48
BRS-TF	10.28±3.29	10.55±5.94	5.22±2.97
BRS-SD	11.39±5.18	15.30±13.82	9.12±10.33

4. Discussion

The state-of-the-art BRS measures implemented in this paper, each have advantages and drawbacks. For instance, the sequence method is calculated based on standardized computations which removes inter-subject and intra subject measurement variability [14]. However, the more increase (decrease) SBP-IBI sequences there are in a recording, the more accurate the estimate of the BRS will be. This requires long duration recordings to have an accurate measure of BRS. Furthermore, the transfer function method is known to detect the impairment of baroreflex function, but has been criticized to reflect exclusively the vagal control of heart rate [14]. Finally, the standard deviation method is a simple and fast measure of baroreflex which have been shown to produce consistent results with other methods [13].

In terms of BRS behavior, acute hypoxia decreased BRS while chronic hypoxia exacerbated this effect. In ALT16, BRS values were approximately half of SL. Breathing a hyperoxic mixture did not alter the BRS at sea level. In ALT1, the effects of hypoxia on BRS were reversed by the hyperoxic mixture, BRS recovered SL values (or even slightly above). In chronic hypoxia, breathing a hyperoxic mixture did not significantly elevate BRS. The behavior was comparable to that of SL in the sense that hyperoxic environment does not alter the BRS after acclimatization hypoxia.

It seems that in acute hypoxia, the baroreflex mechanism partially fails to respond adequately to the low O_2 and CO_2 arterial pressures. After acclimatization, the BRS may have been reset toward lower values (approximately half of sea level values for acclimatization to 5,260 m) and seems to behave comparably to sea level condition.

5. Conclusion

This work studies the effect of hypoxia and hyperoxia on baroreflex sensitivity in acute and chronic hypoxia.

BRS was calculated using four state-of-the-art approaches, which were consistent to each other. In acute hypoxia, we hypothesize a partial failure of the BRS to respond to low O_2 and CO_2 pressures. After acclimatization, the BRS is reset toward lower values and behaves comparably to sea level.

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