

# Assessment of the impact of 10-day intermittent hypoxia on the autonomic control measured by heart rate variability

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**Purpose:** The purpose of this study is to establish the alterations in the activity of the autonomic nervous system (ANS) via heart rate variability (HRV) in subjects exposed to 1 h of exogenous hypoxia for 10 consecutive days. **Methods:** Twelve healthy non-smoker males at mean age of  $29.8 \pm 7.4$  (mean  $\pm$  SD) breathed hypoxic air delivered through hypoxicator ( $\text{FiO}_2 = 12.3\% \pm 1.5\%$ ) for 1 h in 10 consecutive days. Pulse oximetry and electrocardiography were monitored during the visit and HRV was calculated for the entire 1-h hypoxic period. **Results:** Comparing the last hypoxic visit to the first, subjects had higher standard deviation of normal-to-normal interbeat intervals (SDNNs) ( $65.7 \pm 32.5$  vs.  $81.1 \pm 32.0$  ms,  $p = 0.013$ ) and root mean square of successive R–R interval difference (RMSSD) ( $58.1 \pm 30.9$  vs.  $76.5 \pm 34.6$  ms,  $p = 0.029$ ) as well as higher lnTotal power ( $8.1 \pm 1.1$  vs.  $8.5 \pm 0.9$   $\text{ms}^2$ ,  $p = 0.015$ ) and high frequency (lnHF) ( $6.8 \pm 1.3$  vs.  $7.5 \pm 1.2$   $\text{ms}^2$ ,  $p = 0.05$ ) and lower LF/HF ( $2.4 \pm 1.4$  vs.  $1.5 \pm 1.0$ ,  $p = 0.026$ ). Changes in saturation ( $87.0 \pm 7.1$  vs.  $90.8 \pm 5.0\%$ ,  $p = 0.039$ ) and heart rate ( $67.1 \pm 8.9$  vs.  $62.5 \pm 6.0$  beats/min,  $p = 0.040$ ) were also observed. **Conclusions:** Intermittent hypoxic training consisting of 1-h hypoxic exposure for 10 consecutive days could diminish the effects of acute exogenous hypoxia on the ANS characterized by an increased autonomic control (SDNN and total power) with augmentation of the parasympathetic nervous system activity (increased RMSSD and HF and decreased LF/HF). Therefore, it could be applied as a pre-acclimatization technique aiming at an increase in the autonomic control and oxygen saturation in subjects with upcoming sojourn to high altitude.

**Keywords:** altitude, hypoxia, autonomic nervous system, heart rate variability, intermittent hypoxic training, acclimatization

## Introduction

Applied as a training method, exogenous hypoxia leads to a number of adaptations, many of which are related to a change in the activity of the autonomic nervous system (ANS). Since heart rate variability (HRV) is a commonly used method to evaluate the ANS activity (43), it could be used to assess some of the adaptations to exogenous hypoxia.

Intermittent hypoxic training (IHT) refers to the repetitive discontinuous use of normobaric or hypobaric hypoxia lasting minutes to days in an attempt to reproduce some of the key features of altitude acclimatization like increase in oxygen saturation (1) and chemoreceptors' sensitivity (15, 20, 30, 31, 36) and even baroreflex sensitivity in patients with chronic obstructive pulmonary disease and bronchial asthma (44). Intermittent hypoxia is

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also an integral part of mountaineering – climbers ascend to high altitude, stay there before coming back to the base camp, and reach even higher altitudes on their next attempt. IHT is a method designed to reproduce pre-acclimatization in laboratory environment – a process of training the oxygen transporting systems to an upcoming sojourn at high altitude (24, 30), since commercial expeditions are time-restrained and are not always able to follow the routine protocol dictating slow ascent. Other subjects who can benefit from pre-acclimatization are people traveling by plane to high-altitude cities (e.g., The Andes or Tibet) or elite athletes facing competitions at high altitude (42). IHT could be performed by either isobaric or hypobaric hypoxic exposure but always with a limited duration (13, 23).

Some of the adaptations to high altitude require prolonged time. Similarly, the 5% increase in erythrocyte volume may need 3–4 weeks of living at 2,500 m and training at 1,300 m (35). Therefore, these adaptations are difficult to achieve in a laboratory environment. Any pre-acclimatization exclusively influences those mechanisms, which are responsible for the early stages of high-altitude adaptations, i.e., to avoid acute mountain sickness (AMS) if acute ascent was unavoidable. Some of the first alterations to occur [increased saturation and hypoxic ventilatory response (HVR)] correlate with the activity of the ANS (26, 28); therefore, HRV is a reliable tool for estimating the changes observed during the early stages of acclimatization (18, 22, 36, 39).

Long-term adaptations to high altitude (as well as IHT) associated with the ANS activity include an increased chemoreceptor sensitivity (14, 21, 23, 37), as well as an augmented baroreflex (2). Thus, the ANS activity during high-altitude sojourn is gradually shifted to parasympathetic enhancement, supported by HRV results – increased overall variability, especially high frequency (HF) (4, 8, 11).

It has also been hypothesized that HRV combined with the oxygen saturation ( $SpO_2$ ) could be used as an AMS predictor – a decrease in both HRV and  $SpO_2$  at lower altitude is associated with AMS development with further ascent (9, 17, 19). Moreover, positive correlation between HRV and  $SpO_2$  has been found during exogenous hypoxic exposure (22, 46), which indicates that HRV can be used as a tool for assessing the level of stress caused by arterial hypoxemia and desaturation. However, most of the studies related to the effect of hypoxia on ANS and adaptations to high altitude are based on long-lasting protocols, which are hardly applicable in daily practice. In addition, there is no data considering the minimal duration of a protocol that can contribute to better pre-acclimatization. Some studies suggest that short protocols ( $FiO_2 = 13\%$  equivalent to 3,800-m altitude for 5 days 2 h/daily) (3) or 2 h per day for 12 consecutive days at the same altitude (14) may induce significant pre-acclimatization like an increase in HVR, so that we believe that by a short protocol with higher hypoxic dose adaptations in the cardiac autonomic control can be achieved. Therefore, the aim of this study was to establish the alterations in the activity of the ANS via HRV in subjects exposed to a short hypoxic protocol – 1 h of exogenous hypoxia for 10 consecutive days.

## Materials and Methods

### *Participants*

Sixteen healthy non-smoker males at mean age of  $29.84 \pm 7.43$  years (mean  $\pm$  SD) and mean body mass index  $24.3 \pm 2.3$  were included in the study. Inclusion criteria were male gender,

age between 20 and 40 years, and good physical condition, and exclusion criteria were any significant pathologies that can affect the ANS status, smoking, and obesity. The participants were all lowlanders and had never visited an altitude of more than 2,900 m or participated in exogenous hypoxic protocols. All were engaged in regular physical activity (2–4 times weekly). Four subjects discontinued their participation in the study due to premature beats more than 15%, illness, or personal decision to withdraw their informed consent and were excluded from the analysis and 12 men completed the whole protocol. The subjects received all the relevant information about the study, regarding its aim, protocol, and included tests. A signed informed consent was obtained from all the subjects prior to inclusion in the study and a questionnaire about their physical status was filled in.

### *Measurements*

The visits were carried out in the morning between 9 a.m. and 11 a.m. During the experiment and the preceding day, the participants did not take any medications, drink coffee, or alcohol. They abstained from eating at least 2 h prior to the visits. A physical examination including an electrocardiogram reviewed by a cardiologist to exclude cardiovascular abnormalities or any rhythm or conductive disorders was carried out. Four-channel electrocardiography (ECG) (H3+, Mortara Instruments, Milwaukee, USA), pulse oximetry (CMS50F, Contec Medical Systems, Qinhuangdao, China), and manually measured blood pressure (Boso, Bosch and Sohn, Germany) were recorded during the whole visit.

The subjects were situated in supine position in a comfortable bed, placed in a quiet, well-aerated room with constant light and ambient temperature in the absence of any distracting factors. They were instructed to keep calm, motionless, and silent.

The intermittent hypoxic protocol consisted of a 1-h continuous hypoxic exposure for 10 consecutive days. During the first 10 min of every visit, the participants breathed ambient air at an altitude of 130 m (Plovdiv, Bulgaria) to reach a steady-state condition. Subsequently, air with decreased oxygen concentration corresponding to an altitude of about 4,200 m ( $\text{FiO}_2 = 12.3\% \pm 1.5\%$ ) was applied for 1 h via full-face mask, using a hypoxicator (AltiPro 8850 Summit+, Altitude Tech, Canada). This protocol does not include any change in the barometric pressure (normobaric hypoxia).

ECG recordings were reviewed manually and R–R intervals were subsequently extracted automatically by H-Scribe 5 software (Mortara Instruments, Milwaukee, USA). HRV data were analyzed using Kubios HRV software, which automatically computes all commonly used parameters and uses an automatic filter for artifacts and premature beats (43). HRV parameters were derived by analyzing the whole 1-h hypoxic period. Prior to the spectral estimation, beat-to-beat R–R time series were transformed to evenly sampled time series using a cubic spline interpolation. Fast Fourier transform was used for calculation of the frequency domain parameters using Welch's periodogram with a window length of 256 s and 50% overlap.

To compare the effect of the acute hypoxic exposure on HRV, 5-min time intervals were analyzed in normoxic conditions and compared to the last 5 min of hypoxic exposure during the first and last visit of the protocol.

The following parameters were derived from the R–R data: total power (TP) and standard deviation of normal-to-normal interbeat intervals (SDNNs) as measures of overall autonomic regulation, absolute and normalized (normalized units) powers of HF (0.15–0.40 Hz) and low frequency (LF; 0.04–0.15 Hz) spectral components, respectively,

reflecting parasympathetic nervous system (PSNS) activity and combined sympathetic (SNS) and parasympathetic activities. The ratio LF/HF was also calculated as an index of sympatho-vagal balance, although its reliability was challenged recently (7, 40). Root mean square of successive R–R interval difference (RMSSD) is a time domain parameter associated with the parasympathetic activity (short-term beat-to-beat variability) (32).

### Statistical analysis

The statistical analysis was performed using SPSS v.17.0 (IBM corporation, Armonk, NY, USA), using paired-sample *t*-test. Normality of distribution was assessed by Shapiro–Wilks test. Skewness of distribution in some parameters (absolute spectral powers) was normalized with natural logarithmic (ln) transformation. To assess the relationship between SpO<sub>2</sub> and HRV parameters, bivariate, two-tailed, Pearson’s correlation analysis was performed.

The study was presented and approved at a meeting of the institutional ethics committee of Medical University of Plovdiv. The authors report no biomedical financial interests or potential conflicts of interest.

## Results

The effect of the IHT on saturation, heart rate (HR), and basic HRV parameters is presented in Tables I and II as a comparison between their respective baseline (Day 1) and end-of-protocol (Day 10) values. Significant increase in the HF and increase in the TP as well as a decrease in the LF/HF ratio (Fig. 1) were observed for each of the tested subjects, but no significant change was present in the LF. Changes were also present in the time domain parameters – subjects had higher SDNN and RMSSD (Fig. 2) at the end of the study. Oxygen saturation and heart rate were also influenced by the IHT – increased SpO<sub>2</sub> and decreased mean heart rate (MeanHR). No significant difference in arterial blood pressure was detected ( $118.3 \pm 5.4/72.9 \pm 9.6$  vs.  $116.3 \pm 6.4/77.9 \pm 5.0$ ,  $p = 0.210/0.060$ ).

In addition, there was no significant difference in the peak frequencies of HF between the first and the last visit ( $0.20 \pm 0.05$  vs.  $0.19 \pm 0.04$ ,  $p = 0.503$ ).

Table I. Comparison of oxygen saturation and time domain parameters (mean  $\pm$  SD) between the first and the last days of 10-day intermittent hypoxic exposure protocol

Parameter	Protocol		
	Day 1	Day 10	Day 1 vs. Day 10 ( <i>p</i> )
Mean SpO <sub>2</sub> (%)	87.0 $\pm$ 7.1	90.8 $\pm$ 5.0	0.039
MeanHR (beats/min)	67.1 $\pm$ 8.9	62.5 $\pm$ 6.0	0.040
SDNN (ms)	65.7 $\pm$ 32.5	81.1 $\pm$ 32.0	0.013
RMSSD (ms)	58.1 $\pm$ 30.9	76.5 $\pm$ 34.6	0.029

HR: heart rate; RMSSD: root mean square of successive R–R interval difference; SDNN: standard deviation of the intervals between normal beats; SpO<sub>2</sub>: oxygen saturation; RMSSD: root mean square of successive R–R interval difference

Table II. Comparison of frequency domain HRV parameters (mean  $\pm$  SD) between the first and the last days of 10-day intermittent hypoxic exposure protocol

Parameter	Protocol		
	Day 1	Day 10	Day 1 vs. Day 10
lnTotal power (ms <sup>2</sup> )	8.1 $\pm$ 1.1	8.5 $\pm$ 0.9	0.015
lnLF (ms <sup>2</sup> )	7.5 $\pm$ 1.0	7.7 $\pm$ 0.8	0.078
lnHF (ms <sup>2</sup> )	6.8 $\pm$ 1.3	7.5 $\pm$ 1.2	0.026
LF (nu)	66.8 $\pm$ 14.6	55.9 $\pm$ 13.4	0.032
HF (nu)	34.1 $\pm$ 14.5	44.1 $\pm$ 13.4	0.050
LF/HF	2.4 $\pm$ 1.4	1.5 $\pm$ 1.0	0.026

HRV: heart rate variability; SD: standard deviation; HF: high frequency; LF: low frequency; nu: normalized units; ln: natural logarithm

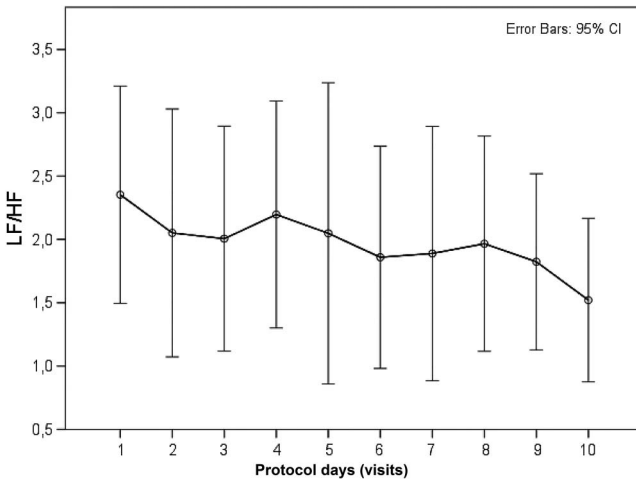


Fig. 1. Changes in low frequency/high frequency (LF/HF) index of heart rate variability during the 10-day hypoxic protocol

When comparing normoxia with the end hypoxic period, there was a significant increase in LF/HF (1.5  $\pm$  0.9 vs. 2.8  $\pm$  1.7,  $p$  = 0.046) and MeanHR (63.6  $\pm$  8.7 vs. 68.4  $\pm$  9.0,  $p$  = 0.016) during the first hypoxic visit, but no change on the last day of the protocol in LF/HF (1.8  $\pm$  1.1 vs. 1.5  $\pm$  1.2,  $p$  = 0.438) or MeanHR (64.2  $\pm$  7.6 vs. 63.3  $\pm$  8.1,  $p$  = 0.590). Overall variability (SDNN) showed a tendency to increase on the first visit (59.7  $\pm$  36.2 vs. 74.1  $\pm$  47.3,  $p$  = 0.88) and a significant increase during the last hypoxic visit (63.2  $\pm$  24.0 vs. 87.2  $\pm$  38.6,  $p$  = 0.006).

No significant difference was found when comparing the pre-hypoxia HRV parameters between the first and the last visit – SDNN (61.5  $\pm$  37.3 vs. 63.2  $\pm$  24.0 ms,  $p$  = 0.801), RMSSD (59.0  $\pm$  34.7 ms,  $p$  = 0.524), and LF/HF (1.5  $\pm$  0.9 vs. 1.7  $\pm$  1.1,  $p$  = 0.502).

A moderately strong positive correlation was found between the SDNN and the SpO<sub>2</sub> ( $\rho$  = 0.654,  $p$  = 0.029) and between RMSSD and SpO<sub>2</sub> ( $\rho$  = 0.732,  $p$  = 0.010) during hypoxic exposure at the last visit of the protocol (Fig. 3).

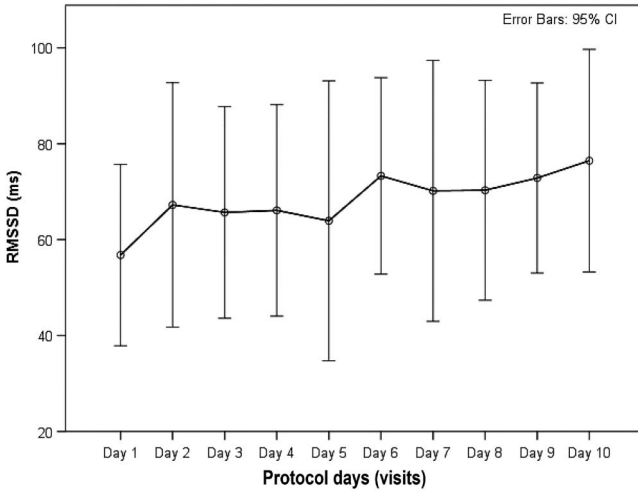


Fig. 2. Changes in root mean square of successive R-R interval difference (RMSSD) during the 10-day hypoxic protocol

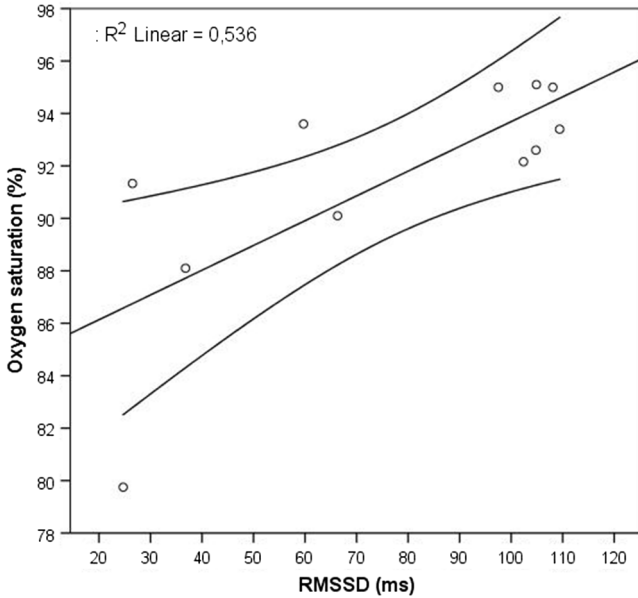


Fig. 3. Correlation between RMSSD and SpO<sub>2</sub> during hypoxic exposure at the last visit of the protocol

### Discussion

The results of this study verify that 1-h daily exposure to exogenous hypoxia corresponding to an altitude of 4,200 m for 10 consecutive days leads to adaptations related to increased SpO<sub>2</sub>, decreased heart rate, and a rise in the overall variability (an increase in the TP and SDNN) mainly due to parasympathetic activation – augmented RMSSD, HF, and a decrease in the LF/HF index.

These results support the statement that IHT is able to decrease the effect of acute exogenous hypoxia on the ANS (2), and effective pre-acclimatization could be accomplished using intermittent hypoxic protocols before an upcoming high-altitude visit. Moreover, some

studies suggest that IHT can induce acclimatization changes even more effectively than chronic hypoxia without the side effects of long-term high-altitude sojourn (4, 30).

It is well known that acute exogenous hypoxia augments the SNS and decreases the vagal activity of the ANS (10, 29), which leads to a decrease in HRV parameters (18, 47). This statement was supported by our results presenting an increase in LF/HF and MeanHR with exposure to exogenous hypoxia during the first day of our protocol. This early shift to sympathetic predominance is associated with fast ventilatory and cardiovascular responses to hypoxia, which are some of the first adaptive mechanisms to high altitude (28). However, this SNS overactivation is a risk factor for long-term complications. Therefore, effective long-term acclimatization is characterized by a progressive shift toward a higher parasympathetic influence, which is a result of reduced sympathetic activation and decreased parasympathetic withdrawal during hypoxic exposure (4, 8). The same increase in the PSNS control is observed at the end of our protocol – a rise in RMSSD and HF implying the applicability of HRV for the assessment of the ANS adaptation to exogenous hypoxia. Moreover, breathing hypoxic air did not cause any further increase in LF/HF or MeanHR compared to normoxic during the last visit, which implies that the acquired adaptations are sufficient enough to prevent sympathetic overactivation.

Sympathetic activation as a result of hypoxic exposure induces ventilatory and cardiovascular responses (12, 30). The initial SNS activation during early stages of hypoxic exposure induces ventilatory and cardiovascular responses including fluctuations in blood pressure (12, 30). These physiological changes can lead to vasoconstriction that immediately sensitizes the arterial baroreceptors, which are proven to be active at high altitude (2, 16). Thus, arterial baroreflex counteracts the effects of the initial SNS activation, caused by acute hypoxia. Increased SDNN, TP, HF, and RMSSD in this study show that ANS adaptations during IHT are most probably the results of increased baroreflex activity.

Some studies show contradictory results regarding the effect of chronic intermittent hypoxia on baroreflex sensitivity (34). However, these studies use intermittent hypoxia protocols, characterized by longer total duration and multiple hypoxia/normoxia shifts, with larger periodical swings in SpO<sub>2</sub> and partial pressure of oxygen (pO<sub>2</sub>), representing intermittent hypoxia in obstructive sleep apnea (OSA). On the other hand, IHT, irrespective of its name, is an example of constant hypoxia, in the sense of absence of large swings and periodicity in SpO<sub>2</sub> and pO<sub>2</sub> during the period of the hypoxic exposure. It could be speculated that these two models of intermittent hypoxia initiate different adaptive mechanisms. Furthermore, patients with OSA have oppressed baroreflex sensitivity (25, 27) in contrast to healthy subjects exposed to exogenous hypoxia (2, 16). On the other hand, sympathetic activation during apnea in patients with OSA aims to increase the vascular peripheral resistance and maintain the blood pressure, which is decreased due to the diminished cardiac preload (41) and baroreflex activation is not necessary. Therefore, it is not appropriate to compare IHT with the intermittent hypoxia in OSA.

Since there is insufficient knowledge about acclimatization by intermittent hypoxia, there is actually no standardized protocol for pre-acclimatization. To date, most of the studies show a significant difference in exposure patterns. Burtscher et al. (8) showed benefits if subjects are exposed for 1–4 h/day to normobaric hypoxia at a corresponding altitude of 4,000 m (FiO<sub>2</sub> = 12%) and some studies suggest that 1 week or even shorter protocols (FiO<sub>2</sub> = 13% equivalent to 3,800 m altitude for 5 days 2 h/daily) may induce significant pre-acclimatization like an increase in HVR (3, 5). There is no data about the changes in the ANS activity and HRV during such short-term IHT protocols. However, this study showed that

such protocols are able to augment the autonomic control characterized by parasympathetic predominance (higher SDNN, TP, RMSSD, and HF and lower LF/HF).

Similar to ours is the protocol of Garcia et al. (14) who simulated an altitude of 3,800 m, 2 h per day for 12 consecutive days. They found increased HVR without changes in the oxygen saturation. However, other authors suggest that the increased HVR contributes to increased ventilation and raise the SpO<sub>2</sub> at the same altitude (24). Even though we did not measure the ventilation, we analyzed the mean peak frequency of HF band of HRV. Thayer et al. (45) have suggested that the central frequency of the HF component may serve as an index of respiratory rate when more direct measures are not available. The peak frequency of the HF band remained constant for all the analyzed periods, which indicates that there were no significant changes in the respiratory rate during the protocol that could potentially affect the HRV results.

It has been proven that lower oxygen saturation, combined with decreased HRV, could be associated with higher risk of AMS during the early stages of hypoxic exposure (9, 19). Therefore, our IHT protocol is able to achieve pre-acclimatization by increasing the autonomic control and SpO<sub>2</sub>. Furthermore, de-acclimatization is slower than acclimatization, because the body response to hypoxia can be “turned on” faster than “turned off” when normoxia is restored (4, 30). Thus, it could be suggested that such a protocol with 1 h of hypoxic exposure for 10 consecutive days is able to decrease the risk of AMS in people with upcoming high-altitude sojourn. However, our protocol did not include further high-altitude visits. After all, two of our tested subjects attacked Lenin Peak (7,134 m) a few days after the protocol and reported that they felt well with no symptoms of AMS.

The significant increase in the overall variability as well as HF and RMSSD (Fig. 2) and the decrease in LF/HF (Fig. 1) observed during the last visit of our protocol are indicative for vagal predominance. This is in concordance with other results, which suggest that acclimatization seems to be characterized by a progressive shift toward a higher parasympathetic tone (3, 6). The improved autonomic control could be potentially beneficial in some chronic cardiovascular and respiratory conditions associated with sympathetic predominance, since it is well known that augmented SNS activity further increases the oxygen demand (33) and other IHT protocols have recently showed positive effects in treatment of major cardiovascular diseases (38).

In addition, we found a positive correlation between the oxygen saturation and SDNN and RMSSD at the last day of the protocol (Fig. 3). Therefore, increased HRV values are associated with higher SpO<sub>2</sub>. Thus, it could be suggested that the intensive ANS activation with parasympathetic predominance is a prerequisite for adequate adaptation to exogenous hypoxia. However, a correlation is not an indicator of positive cause–effect relationship and further investigations are needed to confirm these data.

### *Limitations*

Some limitations of our research should be considered. We did not record the respiratory rate and tidal volume; therefore, we do not have information about ventilation that is known to affect the HRV parameters (44), although the peak frequency of HF [which is suggested as an indirect index of respiratory rate (45)] showed no changes during the different periods of the protocol.

It can be presumed that familiarization with the protocol and the hypoxicator could also lead to a progressive decrease of a stress reaction that can affect HRV findings. However, we compared the prehypoxia HRV parameters between the first and last visit and found no



statistical difference. Therefore, we believe that our findings reflect adaptations to hypoxia itself rather than familiarization with the protocol. The sample of the study is not big enough to produce more explicit results. Increasing the number of enrolled subjects would potentially decrease the impact of confounding factors affecting HRV.

In conclusion, the results of this study show that IHT consisting of 1-h hypoxic exposure for 10 consecutive days could diminish the effects of acute exogenous hypoxia on the ANS characterized by an increased autonomic control (SDNN and TP) with augmentation of the PSNS activity (increased RMSSD, HF, and SD2 and decreased LF/HF). Therefore, it could be applied as a pre-acclimatization technique aiming at an increase in the autonomic control and oxygen saturation in subjects with upcoming sojourn to high altitude.

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### Conflict of interest

The authors declare that they do not have any conflict of interests to disclose.

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