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Assessment of the acute impact of normobaric hypoxia as a part of an intermittent hypoxic training on heart rate variability

Zdravko Taralov[a], Kiril Terziyski[a], Peter Dimov[a], Blagoi Marinov[a], Mika P. Tarvainen[b,c], Renza Perini[d], Stefan Kostianev[a]

[a] *Pathophysiology Department, Medical University of Plovdiv, Plovdiv, Bulgaria*
[b] *Department of Applied Physics, University of Eastern Finland, Kuopio, Finland*
[c] *Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland*
[d] *Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy*

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Výška

SOUHRN

Cíl: Zjistit dynamiku autonomního nervového systému (ANS) pomocí variability srdeční frekvence (heart rate variability, HRV) během akutní expozice normobarické hypoxii a po ní, k níž dochází během jednoho sezení podle protokolu intermitentního hypoxického tréninku.
Materiál a metody: Čtyřiadvacet zdravých mužů ve věku 28,0 ± 7,2 (průměr ± SD) vdechovalo po dobu jedné hodiny hypoxický vzduch (inspirační koncentrace kyslíku [FiO_2] 12,3 ± 1,5 %) z hypoxického generátoru (AltiPro 8850 Summit+, Altitude Tech, Kanada). Před expozicí hypoxii, během ní a po ní se provádělo vyšetření pulsní oxymetrií a měřila se variabilita HRV.
Výsledky: Na konci hypoxického sezení vykazovali všichni hodnocení jedinci vyšší nízkou frekvenci (lnLF) (6,9 ± 1,1 ms² vs. 7,5 ± 1,1 ms²; $p = 0,042$), LF/HF (1,5 ± 0,8 vs. 3,3 ± 2,8; $p = 0,007$) a směrodatnou odchylku 2 na Poincarého mapě (SD2) (92,8 ± 140,0 ms vs. 120,2 ± 54,2 ms; $p = 0,005$) i nárůst celkové síly (7,7 ± 1,1 ms² vs. 8,1 ± 1,2 ms²; $p = 0,032$) a směrodatné odchylky intervalu mezi dvěma normálními tepy (SDNN) (57,3 ± 31,0 ms vs. 72,3 ± 41,1 ms; $p = 0,024$), avšak nižší entropii vzorku (SampEn) (1,6 ± 0,2 vs. 1,4 ± 0,2; $p = 0,010$). Bezprostředně po expozici hypoxii se snížila hodnota LF/HF (3,3 ± 2,8 vs. 2,2 ± 1,8; $p = 0,001$) při současném významném zvýšení lnHF (6,6 ± 1,4 ms² vs. 7,1 ± 1,3 ms²; $p = 0,020$).
Závěr: Akutní normobarická hypoxie jako součást jednoho sezení v rámci tréninkového protokolu intermitentní hypoxie vede ke změnám aktivity ANS. Během expozice hypoxii převažuje tonus sympatiku a okamžitě po zrušení účinku hypoxií indukovaného faktoru dochází k nárůstu tonu parasympatiku.

ABSTRACT

Aim: To assess the dynamics of the autonomic nervous system (ANS) by means of heart rate variability (HRV) during and after acute exposure to normobaric hypoxia, representing a single session of an intermittent hypoxic training protocol.
Material and methods: Twenty four healthy males aged 28.0 ± 7.2 (mean ± SD) breathed hypoxic air (FIO2 = 12.3 ± 1.5%) for one hour delivered via hypoxicator (AltiPro 8850 Summit+, Altitude Tech, Canada). Pulse oximetry and HRV were measured before, during and after the hypoxic exposure.

Address: Dr. Zdravko Zdravkov Taralov MD, Pathophysiology Department, Plovdiv Medical University, 15A Vassil Aprilov Blvd., Plovdiv, Bulgaria,
e-mail: ztaralov@pathophysiology.info
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Intermittent hypoxic training

Results: At the end of the hypoxic session all of the tested subjects had higher low frequency (lnLF) (6.9 ± 1.1 ms^2 vs. 7.5 ± 1.1 ms^2; p = 0.042), LF/HF (1.5 ± 0.8 vs. 3.3 ± 2.8; p = 0.007) and standard deviation 2 of the Poincaré plot (SD2) (92.8 ± 140.0 ms vs. 120.2 ± 54.2 ms; p = 0.005) as well as increase in the Total power (7.7 ± 1.1 ms^2 vs. 8.1 ± 1.2 ms^2; p = 0.032) and the Standard deviation of normal-to-normal interbeat intervals (SDNN) (57.3 ± 31.0 ms vs. 72.3 ± 41.1 ms; p = 0.024) but lower Sample entropy (SampEn) (1.6 ± 0.2 vs. 1.4 ± 0.2; p = 0.010). Immediately after the hypoxic exposure LF/HF lowered (3.3 ± 2.8 vs. 2.2 ± 1.8; p = 0.001) but lnHF significantly increased (6.6 ± 1.4 ms^2 vs. 7.1 ± 1.3 ms^2; p = 0.020).
Conclusion: Acute normobaric hypoxia as a part of a single session of an intermittent hypoxic training protocol leads to changes in the activity of the ANS. The sympathetic tone prevails during hypoxic exposure and parasympathetic tone increases immediately after the hypoxic factor is withdrawn.

Introduction

Intermittent hypoxic training (IHT) has become a very popular method nowadays, enhancing exercise performance, working ability or as a pre-acclimatization alpine technique [1]. It refers to the discontinuous use of normobaric or hypobaric hypoxia, in an attempt to reproduce some of the key features of altitude acclimatization [2]. Prolonged hypoxic exposure for one to several hours a day as a part of the intermittent hypoxic training leads to a number of adaptations in the physiological systems that transport and utilize oxygen [3]. Most of the initial adaptations are related to alterations in the activity of the autonomic nervous system (ANS), such as acceleration of heart rate (HR) almost immediately after hypoxic stimulation [4,5]. Heart rate variability (HRV) is the variation in the beat-to-beat intervals and is commonly used to evaluate the autonomic modulation of the heart, especially sympathetic/parasympathetic interaction.

HRV has been used in the assessment of initial adaptations to hypoxic exposure at high altitude [6–9]. Acute exposure to high altitude has been shown to lead to a decrease in Total power (TP) and standard deviation of normal-to-normal inter-beat intervals (SDNN) that indicates a reduction in the overall HRV associated with an increase in LF/HF ratio, suggesting sympathetic predominance [10–13]. However, in most of the studies in humans, the effect of hypobaric, high altitude hypoxia has been evaluated which is not the case with IHT which is accomplished by means of normobaric hypoxia. Additionally, at high altitude the influence of various ambient factors such as temperature, humidity, sensory stimulation and radiation should be taken into account [14]. Furthermore, there are no studies regarding the ANS immediately after the hypoxic exposure. This article presents our pilot study in this field.

Aim

To assess the dynamics of the ANS by means of heart rate variability during and after acute exposure to normobaric hypoxia, representing a single session of intermittent hypoxic training protocol.

Material and methods

Twenty four healthy non-smoker males aged 28.0 ± 7.2 (mean ± SD) were included in the study. The subjects received all the relevant information about the study, regarding aim, protocol, included tests. A signed informed consent was received from all the subjects prior to inclusion in the study and a questionnaire about their physical status was filled in. During the experiment and the preceding day, the participants did not take any medications, drink coffee or alcohol. A physical examination, including an electrocardiogram (ECG) reviewed by a cardiologist to exclude cardiovascular abnormalities or any rhythm or conductive disorders was carried out. No side effects or complaints were reported during the protocol.

The subjects were situated in supine position in a comfortable bed, placed in a quiet, well aerated room with constant light and ambient temperature and absence of any distracting factors. They were instructed to keep calm without excessive voluntary movement or speaking.

During the first 10 min of the visit the participants breathed ambient air, i.e. at altitude of 130 m (Plovdiv, Bulgaria). Subsequently, air with an oxygen concentration of 12.3 ± 1.5% corresponding to altitude of 4 200 m was administered for one hour via full-facemask, using a hypoxicator (AltiPro 8850 Summit+, Altitude Tech, Canada). This protocol did not include any change in the barometric pressure (normobaric hypoxia). After the end of the hypoxic session the mask was removed and the subject breathed ambient air for 10 min.

Four-channel ECG (H3+, Mortara Instruments, Milwaukee, USA), pulse oximetry (CMS50F, Contec Medical Systems, Qinhuangdao, China) were recorded during the whole protocol. Blood pressure was manually measured on every 10 min (Boso, Bosch and Sohn, Germany).

ECG recordings were reviewed, R–R intervals were extracted automatically by H-Scribe 5 software (Mortara Instruments, Milwaukee, USA). Five-minute samples were selected from the end of the pre-hypoxic period; the beginning of hypoxia the end of hypoxia and immediately after the hypoxic exposure for the subsequent analysis. After removing trends, data were analyzed using Kubios HRV software [15] by which both time and frequency domain parameters were calculated. Prior to the spectral estimation by Fast Fourier Transform, beat-to-beat RR time series were transformed to evenly sampled time series using a cubic spline interpolation.

The following parameters were derived from the RR data: TP and SDNN as measures of overall autonomic regulation; absolute and normalized (nu) powers of high frequency (HF; 0.15–0.40 Hz) and low frequency (LF; 0.04–0.15 Hz) spectral components, respectively reflecting parasympathetic nervous system (PNS) activity and combined sym-

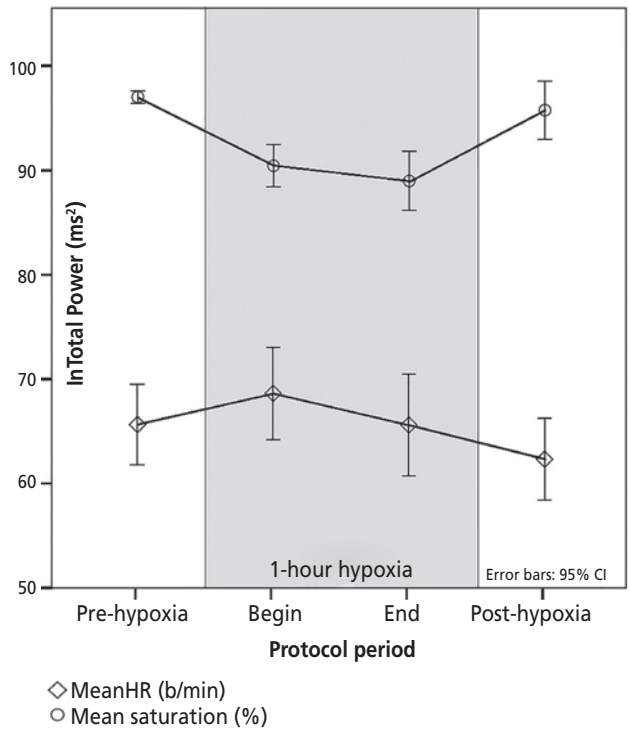

Fig. 1 – Dynamics of the Mean Heart Rate and oxygen saturation before, during and after the hypoxic exposure. MeanHR – Mean heart rate.

pathetic (SNS) and PNS activities. The ratio LF/HF was also calculated as an index of sympatho-vagal balance. Root mean square of successive RR interval difference (RMSSD) is a time domain parameter associated with the parasympathetic activity [16]. In addition to linear methods described above, three commonly used nonlinear parameters were computed. These include standard deviations SD1 and SD2 of the Poincaré plot – SD1 related to fast beat-to-beat variability in data and SD2 describing longer-term variability of R–R [17]. Sample Entropy (SampEn) was also computed and provides a simple index for the overall complexity and predictability of HRV time series [18].

The statistical analysis was performed using repeated measures one-way ANOVA (SPSS v.17.0). Normality of distribution was checked by Kolmogorov-Smirnov test. Skewness of distribution in some parameters (absolute spectral powers) was normalized with natural logarithmic transformation.

The study was presented and approved at a meeting of the Institutional Ethics Committee of Medical University of Plovdiv.

Results

In response to the hypoxic exposure the oxygen saturation (SpO_2) decreased abruptly from 97.0 ± 1.3% to 91.1 ± 4.4%; $p < 0.001$ and continued to fall during the course of the hypoxic exposure reaching at the end a value of 88.7 ± 6.0% ($p = 0.051$). In the post-hypoxic period a significant increase in SpO_2 to 95.8 ± 6.2% occurred (Fig. 1)

Mean heart rate (MeanHR, Fig. 1) increased significantly in the beginning of the hypoxic exposure from 65.9 ± 8.7 b/min to 68.9 ± 10.0 b/min ($p = 0.033$), but returned to values not different from baseline at the end of the hypoxia (65.8 ± 11.0 b/min). A further decrease in MeanHR to 62.5 ± 8.8 ($p = 0.004$) was observed during recovery. There was no significant change in the blood pressure – 117.4 ± 9.4/75.5 ± 7.1 mmHg pre-hypoxic vs. 116.8 ± 8.3/75.7 ± 8.0 mmHg during the hypoxia.

The results from the HRV analysis are presented in Table 1. Total power and SDNN changes during the different periods are shown in Fig. 2. Total power and SDNN steadily increased under hypoxic conditions, reaching significantly higher values at the end of hypoxia compared to the pre-hypoxic period. RMSSD did not change during hypoxia but significantly increased in the post-hypoxic period.

When dividing the total spectral power into low and high frequency components it was observed that LF power (lnLF) increased with hypoxia exposure and reached

Table 1 – Frequency domain and non-linear parameters at baseline (Pre-hypoxia), beginning of hypoxia, end of hypoxia and after its cessation (Post-hypoxia).

	(1) Pre-hypoxia Mean ± SD	(2) Begin of hypoxia Mean ± SD	(3) End of hypoxia Mean ± SD	(4) Post-hypoxia Mean ± SD	1vs2 *p* value	1vs3 *p* value	2vs3 *p* value	3vs4 *p* value
SDNN (ms)	57.3 ± 31.0	57.3 ± 24.6	72.3 ± 41.2	84.7 ± 40.0	1.000	0.024	0.052	0.222
RMSSD (ms)	55.9 ± 32.9	49.5 ± 26.3	61.9 ± 40.2	71.4 ± 46.1	0.588	1.000	0.137	0.036
lnTotal power (ms^2)	7.7 ± 1.1	7.8 ± 0.9	8.1 ± 1.2	8.5 ± 1.0	1.000	0.032	0.255	0.377
lnLF (ms^2)	6.9 ± 1.1	7.1 ± 0.9	7.5 ± 1.1	7.6 ± 0.9	1.000	0.042	0.358	1.000
lnHF (ms^2)	6.6 ± 1.3	6.4 ± 1.1	6.6 ± 1.4	7.1 ± 1.3	0.778	1.000	1.000	0.020
LF/HF	1.5 ± 0.8	3.0 ± 2.3	3.3 ± 2.8	2.2 ± 1.8	0.035	0.007	1.000	0.001
SD1 (ms)	41.4 ± 23.3	37.1 ± 45.6	45.6 ± 28.4	51.4 ± 33.0	0.520	1.000	0.174	0.097
SD2 (ms)	92.8 ± 40.0	89.5 ± 35.2	120.2 ± 54.2	139.6 ± 54.2	1.000	0.005	0.006	0.099
SampEn	1.6 ± 0.2	1.5 ± 0.3	1.4 ± 0.2	1.3 ± 0.2	1.000	0.010	0.177	1.000

lnHF – HF power; lnLF – LF power; RMSSD – root mean square of successive RR interval difference; SampEn – Sample entropy; SD1 – standard deviation related to fast beat-to-beat variability in data; SD2 – standard deviation describing longer-term variability of R–R; SDNN – standard deviation of normal-to-normal interbeat interval.

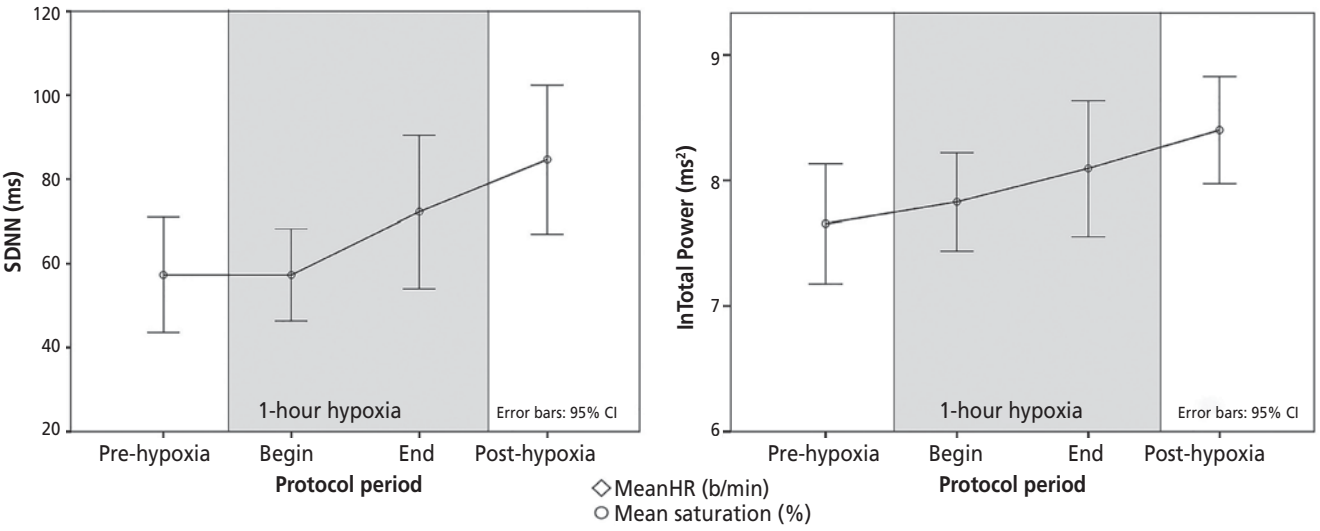

Fig. 2 – Dynamics of the Total power and SDNN before, during and after the hypoxic exposure. SDNN – standard deviation of normal-to-normal interbeat interval.

significantly higher values than in pre-hypoxia at the end of the hypoxic protocol min. No further change was found in the post hypoxic period. The HF power (lnHF) on the other hand had showed no modification during the hypoxia, but increased significantly in the post hypoxic period. When looking at spectral component powers in normalized units, LF/HF ratio changed accordingly, doubling during hypoxia exposure, and decreasing toward initial values after removal of the hypoxic stimulus.

Peak frequency for HF at the four different stages of the study was as follows: before (0.21 ± 0.06), at the beginning (0.20 ± 0.05), at the end (0.21 ± 0.07) and after hypoxia (0.21 ± 0.05) and did not show significant difference (p = 1.000).

The results from non-linear analysis showed significant increase in SD2 and decrease in SampEn at the end of the hypoxic period.

A moderate positive correlation was found between the lnTP and the SpO_2 at the end of the hypoxic period, (rho = 0.597, p= 0.03) and between lnTP at the beginning and SpO_2 at the end of the hypoxic exposure (rho = 0.497, p = 0.019).

Discussion

The results of our study verify the sympathetic predominance during acute exposure to hypoxia expressed in rise in HR, lnLF and higher LF/HF, which are concordant with most of the studies on the topic [2,7,19]. Sympathetic activation is a result of the decreased oxygen saturation and activation of the peripheral chemoreceptors, which leads to increase in heart rate and peripheral vasoconstriction [6,14,20].

Vigo et al. found a different pattern of diminished HRV parameters in low and high frequencies during hypoxia, without any significant changes in LF/HF. However, their protocol is associated with severe hypoxic conditions (extreme altitude of 8230m simulated in hypobaric chamber) which are much more stressful for the organism [21].

We found a significant increase in the TP during hypoxia (predominantly due to increased LF) and SDNN, which differs with the findings of other studies [22–25]. For example, Kanai et al. have measured HRV among untrained office workers and found that the power of HF and LF decreases with increasing altitude but LF/HF rises [7].

However, the hypoxic protocols of the mentioned studies differ significantly from ours in using hypobaric hypoxia and not measuring HRV immediately after hypoxic exposure. Zuzewicz et al. demonstrated that the low barometric pressure is responsible for the decrease in HRV spectral power parameters by comparing the effects of hypobaric and normobaric hypoxic conditions, corresponding to 4500 m altitude [26]. It has been hypothesized that the arterial baroreflex can be a major- although not exclusive- determinant of the HRV and particularly of LF under such circumstances. Moreover, baroreceptor control of the heart is still active at high altitude, counteracting the increase in blood pressure and peripheral vasoconstriction induced by arterial chemoreceptors [6,14,20]. Thus, baroreflex activity could be another possible explanation of the increasing SDNN and Total power during hypoxic conditions since there was no significant change in the arterial pressure.

On the other hand these differences may be attributed to imparity between the study conditions. While our protocol is laboratory based, the studies finding low SDNN and Total power [22–25] are field research. At high altitude other factors, such as temperature, humidity, sensory stimulation and radiation may influence ANS status and should not be underestimated [14]. Our hypothesis is that the observed changes in HRV parameters in our study reflect solely the hypoxic influence. Furthermore, the definition of "acute hypoxia" is quite volatile among different studies, especially regarding its duration, which may also account for the difference in the results. For example, the low responsiveness of the ANS at high altitude is believed to be a protective adaptation mechanism against excessive and continuous sympathetic stimulation in a long-term stay at high altitude [24]. This is a likely

explanation of the lack of changes in long-term HRV variations (lnLF and SD2) in the beginning of hypoxia, but significant increase after one hour of hypoxic exposure, present in our study.

Buchheit et al. have measured the effect of acute hypoxia on HRV in laboratory conditions in seated position. They found a pattern of decreased vagal activity (decreased RMSSD and HF), and sympathetic predominance (LF/HF), but no change in LF, SDNN and TP [27]. The difference from our results could be attributed to the posture, since seated position has been associated with decreased HRV compared to supine position [28].

TP was also increased during the first day of high altitude exposure in the study of Lipsitz et al., who had suggested that the increase in LF power is not simply a result of sympathetic modulation of heart rate, but relates to distinctive cardiopulmonary oscillations associated with alternating periods of hyperpnoea and apnoea [29]. However, our protocol does not include any sleep period and such breathing abnormalities are not likely to occur. Another limitation of our study was that we did not measure breathing frequency and other ventilatory parameters of the subjects during the protocol. However, Thayer et al. have suggested that the central frequency of HF component may serve as an index of respiratory frequency when more direct measures are not available [30]. The peak frequency at the HF band was on average between 0.20–0.21 Hz for all the analyzed time periods, which indicates that there were no significant changes in the respiratory frequency during the protocol that could potentially affect the HRV results.

We observed significant augmentation in RMSSD immediately after the withdrawal of the hypoxic stimulus and a decrease in LF/HF. Absolute power of LF did not change in the post-hypoxic period in contrast to the significantly increased HF. These results suggest an increase in the PSNS activity following the transition from hypoxic to normoxic conditions which also leads to a significant decrease in the MeanHR.

There are very few studies regarding the effect of acute hypoxia on non-linear characteristics of HRV time series and the results are controversial. While Zhang et al. found increased Sample entropy (indicating increased complexity) of HRV in acute hypoxia, Yuanyuan et al. did not observe any change in this parameter [31,32]. We established a pattern of progressively decreasing sample entropy during the hypoxic exposure. These controversies clearly demand further studies in the field to elucidate the effect of hypoxia on non-linear HRV dynamics and clarify their interpretation.

We also found a positive correlation between the oxygen saturation and the total power at the end of hypoxic exposure. It is shown that increased lnTP values are associated with higher SpO_2. Thus, it could be suggested that the intensive ANS activation is a prerequisite for adequate adaptation to exogenous hypoxia. What is more, the positive correlation between lnTP at the beginning of hypoxia and SpO_2 at the end of the one-hour exposure may indicate that just like the good hypoxic ventilatory response [19,24], intense early ANS activation may contribute to higher oxygen saturation during the later stages of hypoxic exposure. However, a correlation is not an indicator of positive relationship and further investigations are needed to confirm these data.

We think that our data may have practical significance. As AMS is a result of a blunted response of the ANS to hypoxia [13] HRV could be used as a predictor for AMS prior to the manifestation of clinical signs [19]. Therefore, our protocol may be potentially used as a predictive laboratory test for AMS, adaptations to hypoxia or the effect of intermittent hypoxic training, but specific investigations focusing on these particular outcomes are needed.

Conclusion

Acute normobaric hypoxia as a part of a single session of an intermittent hypoxic training protocol leads to changes in the activity of the ANS. The SNS tone prevails during hypoxic exposure and PNS tone increases immediately after the hypoxic factor is withdrawn.

The HRV method is reliable and is able to assess the changes in the ANS caused by IHT.

This is our pilot study and further investigation is needed to assess the changes of the autonomic nervous system activity over time with continuous intermittent hypoxic training.

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

Funding body
The study was accomplished with financial support from the Medical University of Plovdiv.

Ethical statement
The study was presented and approved at a meeting of the Institutional Ethics Committee of Medical University of Plovdiv.

Informed consent
A signed informed consent was received from all the subjects prior to inclusion in the study and a questionnaire about their physical status was filled in.

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