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A programme based on repeated hypoxia–hyperoxia exposure and light exercise enhances performance in athletes with overtraining syndrome: a pilot study

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Summary

Overtraining syndrome (OTS) is a major concern among endurance athletes and is a leading cause in preventing them to perform for long periods. Intermittent exposure to hypoxia has been shown to be an effective way of improving performance without exercising. Aim of this pilot study was to evaluate intermittent hypoxia–hyperoxia training combined with light exercise as an intervention to facilitate athletes with OTS to restore their usual performance level. Thirty-four track and field athletes were recruited: 15 athletes with OTS volunteered to participate and undertook a conditioning programme consisting of repeated exposures to hypoxia (O_2 at 10%) and hyperoxia (O_2 at 30%) (6–8 cycles, total time 45 min–1 h), three times a week, delivered 1·5–2 h after a low-intensity exercise session (2 bouts of 30 min, running at 50% of VO_{2max} with 10 min rest between bouts) over 4 weeks. Nineteen healthy track and field athletes volunteered to participate as a control group and followed their usual training schedule. Measurements before and after the intervention included exercise capacity, analysis of heart rate variability and hematological parameters. In athletes with OTS, a 4-week light exercise combined with intermittent hypoxia–hyperoxia training improved exercise performance (191·9 ± 26·9 W versus 170·8 ± 44·8 W in exercise capacity test, $P = 0·01$). Heart rate variability analysis revealed an improved sympatho-parasympathetic index (low frequency/high frequency ratio, 8·01 ± 7·51 before and 1·45 ± 1·71 after, $P = 0·007$). Hematological parameters were unchanged. Our pilot study showed that intermittent hypoxia–hyperoxia training and low-intensity exercise can facilitate functional recovery among athletes with OTS in a relatively short time.

Introduction

Overtraining syndrome (OTS) and non-functional overreaching (NFOR) are a major concern among athletes, coaches and sport medicine doctors. The OTS is a clinical condition, usually triggered by an excessive training load coupled with inadequate recovery, affecting multiple body systems (autonomic nervous, endocrine, immune) with symptoms such as disturbances in mood state, lack of motivation to practice, lack of mental concentration, irritability, depression and sleep disturbances (insomnia, awakening unrefreshed/tired). According to a recently published European College of Sport Sciences and American College of Sport Medicine joint consensus statement, the OTS is characterized by a multifactorial aetiology resulting in underperformance and 'the key indicator of the OTS can be considered an unexplainable decrease in performance'. The same consensus statement also pointed out that the diagnosis of OTS should be made after excluding clinical conditions usually associated with a decrease in performance and 'performance test is considered to be essential for the diagnosis of the OTS' (Meeusen *et al.*, 2013). The concept of decreased performance is central to the diagnosing process, so much so that some authors have suggested the OTS to be renamed 'unexplained underperformance syndrome' (Budgett *et al.*, 2000). Prevalences of NFOR and OTS are relevant in runners (Morgan *et al.*, 1987), swimmers (Morgan *et al.*, 1988) and other endurance sports athletes (Lehmann *et al.*, 1993). Recovery from these conditions usually lasts for weeks (NFOR) or months (OTS) as the functioning of various body systems such as the autonomic nervous system (ANS) and the

neuroendocrine one is impaired (Urhausen *et al.*, 1998; Hynynen *et al.*, 2008).

Repeated intermittent systemic exposure to hypoxia, a treatment known as intermittent hypoxic training (IHT), has been shown to enhance exercise capacity and performance in endurance athletes (Czuba *et al.*, 2011), by determining hematological and non-hematological adaptations (Hamlin & Hellemans, 2007), and to improve cardiopulmonary efficiency and running economy in athletes (Katayama *et al.*, 2004; Burtscher *et al.*, 2010). Also, exposure to hypoxia alternated with periods of exposure to normoxia (IHT) has been found to be efficacious in coronary artery diseases and chronic obstructive pulmonary diseases in patients to improve their tolerance to physical exertion without exercising (Burtscher *et al.*, 2007) and to improve autonomic cardiovascular control (Haider *et al.*, 2009).Based on this findings, a new form of hypoxia exposure (Intermittent Hypoxia-Hyperoxia Training, IHHT), featuring recovery periods consisting of breathing a hyperoxic gas mixture, has been recently introduced and tested in a study aiming at enhancing exercise tolerance and re-balancing the ANS in patients with coronary artery disease (Glazachev *et al.*, 2013). This new approach was designed taking into consideration that breathing a hyperoxic gas mixture allows for quicker oxygen saturation after being exposed to hypoxia, potentially reducing the time of the hypoxic–hyperoxic exposure cycle. At the same time, it has been seen in animal model studies that when normoxia is replaced by hyperoxia within a cycle of hypoxia exposure, there is a stronger stimulus to enhance reactive oxygen species signalling and this form of exposure results in a better resistance of membrane structures and improved antioxidant capacity (Sazontova & Arkhipenko, 2009); this aspect could be relevant in OTS athletes in the light of a recently published research showing that in these athletes, oxidative stress and antioxidant capacity responses to exercise are attenuated (Tanskanen, 2010).

Aim of this pilot study is to evaluate the effects on exercise capacity of a new approach consisting of exposing athletes suffering from OTS to light exercise and repeated intermittence to hypoxia–hyperoxia.

Methods

Thirty-four young track and field athletes (14 men and 20 women, aged 18–20, body weight 71·4 ± 6·9 kg, height 176·4 ± 14·6 cm, 7–9 years sports experience) volunteered to participate in this study. The study protocol was approved by the Ethics Committee of I.M. Sechenov First Moscow State Medical University. All participants gave written informed consent to participate in the study. Athletes did not receive any reimbursement for participation and were asked to keep their usual normal diet/nutrition habits. Study protocol and informed consent were in accordance with the World Medical Association Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/17c.pdf). Athletes diagnosed with OTS were allocated to the OTS group (OTS, n = 15, 7 men), while healthy athletes (HA) were recruited as control group (HA, n = 19, 7 males). The diagnosis of OTS was made by physicians according to the checklist suggested by the ECSS/ACSM experts of the joint consensus group, and other clinical conditions were ruled out as explanation for decreased performance.

Participants were recruited over the course of one sport season from a homogeneous group of track and field athletes. Coaches identified athletes potentially eligible, and physicians assessed potential participants' medical and psychological (negative moods) conditions using the checklist proposed by the ECSS/ACSM consensus experts. Clinicians assessed athletes' moods by asking specific questions related to athletes' perceived chronic fatigue, perceived recovery, lack of motivation to practice, difficulties in being focused, irritability, and sleep quality. Clinicians told the potentially overtrained athletes to stop training, to avoid physically demanding activities, and to 'rest and sleep' as much as possible. After 4 weeks of rest, athletes failing a PWC170 fitness test were allocated to OTS group. None of the participants took any medications before or during the study. Athletes in the HA kept training as usual following their season schedule.

Participants were assessed as follows. In order to tailor the IHHT on individual responses, each athlete's individual sensitivity to hypoxia was assessed in a 10-min hypoxic test (HT), consisting of breathing a hypoxic gas mixture with low oxygen content (10% O_2) through a facial mask while sitting in an armchair. Pulse rate and arterial oxygen saturation (SaO_2) were monitored by pulse oximeter, and data collected were used to define the hypoxia–hyperoxia exposure protocol. Gas mixtures (10–30% O_2) were generated, monitored and delivered to the participants using a prototype version of the Reoxy unit (AI Mediq S.A., Luxembourg City, Luxembourg). A second HT was repeated 3–4 days after completing IHHT to assess hypoxic tolerance dynamics.

IHHT included 5- to 7-min exposure to a hypoxic gas mixture (11% O_2) followed by 2- to 3-min exposure to a hyperoxic (30% O_2) gas mixture without removing the mask. Each session (40–50 min) included 6–8 hypoxia–hyperoxia cycles and was delivered three times a week. IHHT was performed 1·5–2 h after low-intensity training (2 bouts of 30 min running at 50% VO_{2max}, with 10 min rest between bouts).

Exercise performance was tested in sessions taking place in the morning (not earlier than 2 h after breakfast), and physical working capacity was determined using a two-step progressive exercise test on a cycle ergometer (Monark 828E Test Ergometer, Vansbro, Sweden), according to PWC170 protocol (Boreham *et al.*, 1990). Haemodynamic status, including blood pressure (BP) and heart rate (HR), was monitored noninvasively using oscillometric cuffs (Dixtal, DX 2710, Sao Paulo, Brazil) and a heart rate monitor (Polar 810s; PolarElectro, Kempele, Finland). PWC170 and parameters of cardiopulmonary efficiency (IRI, inotropic reserve index; CRI, chronotropic reserve index) were calculated.

The assessments also included an evaluation of the ANS status performed by analysing heart rate variability (HRV) accord-

ing to internationally standardized methods (Task force of ESC and NASPE, 1996). Heart rate variability was estimated by power spectral analysis of the RR intervals (5-min period). Pneumograms and cardiac intervals were simultaneously recorded so that respiratory rate and HR were known to refine the interpretation of the changes in the HF component. Measurements of temporal characteristics of HRV included estimation of HR (bpm), standard deviation of RR intervals (SD, ms) and coefficient of variation (CV, %). Spectral analysis of HRV included determination of total power of the spectrum (TP) of HRV and frequency domain analysis components (high frequency, HF, low frequency, LF, and very low frequency, VLF, expressed as percentage). These parameters as well as the sympatho-parasympathetic index (LF/HF) were calculated as suggested in previously published research among athletes (De Vito *et al.*, 2002) using a dedicated device (Mikhailov, 2000) (ANS – Spektr Device, LLC "Neurosoft", Moscow, Russia).

Performance, hypoxia response and HRV were assessed in both OTS and HA groups, while blood samples were collected and analysed in OTS group only (red blood cells count, reticulocyte count, haemoglobin concentration, haematocrit).

Data were first tested for distribution normality and variance homogeneity. Continuous data are presented as mean ± standard deviation. Wilcoxon matched pairs test was used to compare pre-IHHT to post-IHHT performance, pre-IHHT to post-IHHT autonomic and pre-IHHT to post-IHHT hematological parameters measured in OTS athletes. Mann–Whitney U-test was chosen to compare OTS group to HA group. All statistical analyses were performed using SPSS, Version 15.0, Chicago, SPSS Inc. USA. A two-sided P-value of $<0{\cdot}05$ was set as statistically significant.

Results

Exercise capacity of the OTS athletes was significantly improved after the intervention (IHHT and sport-specific training at low intensity). PWC170 in OTS group was improved by 20 W after 4 weeks of treatment. It is worth noting here that after treatment, OTS athletes showed a performance level (PWC170 = 191·9 ± 26·9 W) that was not different compared to HA at baseline (204·2 ± 13·8 W), but still lower than in HA group after training (278·0 ± 19·3 W, P = 0·023). Chronotropic reserve index and IRI were significantly improved after treatment, suggesting a more efficient systemic cardiovascular performance. At the end of the 4-week treatment, IRI and CRI in OTS group were not significantly different to those recorded in HA group at baseline (Table 1).

Interestingly, haematological parameters were unchanged after the intervention: haemoglobin was 138·3 ± 2·6 g l^{-1} before and 140·7 ± 2·7 g l^{-1} after (not Significant, NS); haematocrit 40·5 ± 0·7% before and 41·6 ± 0·7% after (NS); erythrocytes 4·82 ± 0·09 (10^{12} l^{-1}) before and 4·84 ± 0·09 (10^{12} l^{-1}) after (NS); and reticulocyte count 0·905 ± 0·115% before and 0·979 ± 0·109% after (NS).

Enhanced exercise capacity in OTS athletes after IHHT combined with low-intensity sport-specific training was associated with significant increase of hypoxic tolerance in HT. Blood oxygen desaturation and HR during HT improved significantly after the programme. These values were similar to those recorded in HA at baseline (Table 2).

In cardiac autonomic control parameters, LF and HF power significantly decreased and increased, respectively, compared to pre-programme values. LF/HF ratio decreased, suggesting a relatively stronger parasympathetic drive and reduced sympathetic tone after the programme in OTS athletes. Table 3 shows HRV analysis parameters.

Discussion

Our preliminary data show for the first time that treating athletes with OTS by exposing them to repeated cycles of hypoxia–hyperoxia and light sport-specific exercise is efficacious to improve their level of performance over a relatively short period of time and to counteract some of the OTS features. After completing the programme, all OTS athletes showed significantly improved tolerance to exercise without significant hematological changes; our findings are consistent with the results of other studies using hypoxia–normoxia exposure as an intervention to improve aerobic capacity in patients

Table 1 Performance parameters.

	OTS Pre-value	OTS Post-value	*P*-value	HA baseline	HA post-training
PWC170(W)	170·8 ± 44·8	191·9 ± 26·9	0·01	204·2 ± 13·8*	278·0 ± 19·3**
IRI (%)	65·8 ± 3·6	54·8 ± 5·4	0·008	50·8 ± 4·1*	49·6 ± 3·8**
CRI (%)	50·0 ± 5·3	38·0 ± 5·9	0·01	37·5 ± 4·9*	36·8 ± 5·0

OTS, overtraining athletes; HA, healthy athletes.
Performance parameters at baseline and after a 4-week treatment in athletes with overtraining syndrome (OTS, n = 15) and in healthy athletes (HA, n = 19). Values are mean ± standard deviation. P-values refer to pre- versus postintervention in OTS group. IRI was calculated as $(SBP_{max} - SBP_{rest})/SBP_{rest}$. CRI was calculated as $(HR_{max} - HR_{rest})/HR_{rest}$.
*Significantly ($P \leq 0{\cdot}05$) different from OTS pre values.
**Significantly ($P \leq 0{\cdot}05$) different from OTS post values.

Table 2 Physiological responses to hypoxic test.

	OTS (n = 15)			HA (n = 19)	
	Pre	**Post**	***P*-value**	**Baseline**	**Post-training**
$SaO_{2\ min}$,%	77·9 ± 6·8	84·2 ± 5·7	0·001	83·7 ± 9·0*	85·7 ± 12·6
HR_{max},bpm	82·2 ± 14·6	76·6 ± 11·0	0·010	79·7 ± 13·1*	76·7 ± 9·4
ΔSaO_2, %	−19·3 ± 7·9	−12·2 ± 5·7	0·002	−14·7 ± 13·0	−12·7 ± 9·0
ΔHR, bpm	14·6 ± 10·2	9·1 ± 8·2	0·016	9·7 ± 7·5*	10·0 ± 2·4

OTS, overtraining athletes; HA, healthy athletes.
Physiological responses to hypoxic test (FiO_2 = 10%, 10 min of continuous exposure) in 15 overtrained athletes (OTS) and 19 healthy athletes (HA). Values are mean ± standard deviation. $SaO_{2\ min}$ (minimum oxygen saturation of blood during hypoxic test exposure) and HR_{max} (maximum HR during HT), respectively; ΔSaO_2 and ΔHR – mean values of arterial oxygen desaturation and increment of HR in HT compared to normobaric normoxic condition. In brackets, P-values related to pre- versus postintervention results in OTS group.
*Significantly ($P \leq 0{\cdot}05$) different from OTS pre values.

Table 3 Heart rate variability analysis.

	OTS pre	**OTS post**	***P*-value**	**HA pre**	**HA post**
RR, ms	880 ± 160	890 ± 120	NS	955 ± 160	990 ± 180**
SD, ms	54·0 ± 24·7	76·0 ± 26·8	0·03	82·0 ± 24·8*	79·0 ± 31·0
$HR_{at\ rest}$, bpm	68·2 ± 19·6	67·12 ± 13·7	NS	62·4 ± 3·8	60·4 ± 4·6**
TP, ms^2	3118 ± 1687	3890 ± 1246	NS	4503 ± 512*	4654 ± 521
VLF, ms^2	1410 ± 754	1298 ± 503	NS	1610 ± 315	1740 ± 404
LF, ms^2	1300 ± 661	801 ± 673	0·005	860 ± 340	828 ± 420
HF, ms^2	277 ± 188	624 ± 468	0·005	1100 ± 344*·**	1167 ± 501**
LF/HF	8·01 ± 7·51	1·45 ± 1·71	0·007	2·2 ± 1·0*	1·81 ± 0·95

OTS, overtraining athletes; HA, healthy athletes; bpm, beats per minute; RR, R-R intervals variability; SD, standard deviation of R-R intervals; HR, heart rate; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF, index. P-values refer to comparing pre versus post intervention values in OTS group.
*Significantly ($P \leq 0{\cdot}05$) different from OTS pre values.
**Significantly ($P \leq 0{\cdot}05$) different from OTS post values.

(Burtscher *et al.*, 2007) and endurance athletes (Katayama *et al.*, 2004; Hamlin & Hellemans, 2007; Burtscher *et al.*, 2010). As well, cardiovascular response to a 10-min continuous HT was also improved and similar to the one recorded in HA. Reduced HR and systolic BP values suggest an increase in the overall cardiovascular efficiency after this novel treatment. One may have reservations about including exercise to the treatment, so making it difficult to differentiate between the effects due to hypoxic–hyperoxic exposure and those potentially caused by exercise. The reason why we added light intensity sport-specific exercise (running) to the treatment plan was mainly based on the fact that, in our experience, athletes told to stop for a long time (e.g. 4 weeks at least) usually perceive this medical advice as a further proof of their condition severity, so potentially affecting their psychological status. Thus, after 4 weeks of total rest, adding light exercise sessions was a strategy to minimize the psychological impact of the diagnosis (OTS) on athletes mood and to keep them committed and focused. In addition, while there is evidence that intermittent hypoxia exposure improves performance in HA, cardiac patients and pulmonary patients, to the best of our knowledge, there is no evidence that low-intensity training can be useful to improve performance in athletes diagnosed with OTS. Instead, the rest is the best available treatment option for people suffering from OTS and reduced training loads might be an option only in overreaching athletes, according to the ECSS/ACSM joint consensus. As athletes with OTS have shown a reduced cardiac autonomic modulation (Hynynen *et al.*, 2008) and rebalancing cardiovascular autonomic control by reducing its sympathetic overdriving component which has been proven to be associated with intermittent hypoxic exposure (Haider *et al.*, 2009), we would like to suggest a recovered ANS balance as a partial explanation of our findings. Another potential contribution to explain our promising results could be linked to the role of oxidative stress/antioxidant capacity. Muscular exercise is known to increase oxidative stress, free radical production and, as part of the physiological process of adaptations to adequate training loads, athletes' body antioxidant capacity (Finaud *et al.*, 2006). Only recently, an altered response to oxidative stress was found to be associated with training overload, and athletes' impaired antioxidant capacity has been suggested to play a role in the pathophysiology of NFOR/OTS (Margonis *et al.*, 2007; Tanskanen *et al.*, 2010).The mechanisms behind 'the unexplainable decreased performance' has not been identified yet, but several studies on animal models provide a rationale

to support hypoxia–hyperoxia exposure as a potential way of conditioning athletes body to better cope with oxidative stress. These studies have demonstrated that exposure to hypoxia triggers adaptations enhancing total antioxidant capacity (Sazontova *et al.*, 1987, 1994; Sazontova & Arkhipenko, 2009). Moreover, by replacing normoxic with hyperoxic gas mixtures (IHHT), it is possible to generate a stronger stimulus shown to evoke more pronounced adaptive responses than IHT (Arkhipenko *et al.*, 1997).Cellular and tissue adaptations triggered by systemically exposing athletes to hypoxia–hyperoxia short cycles are likely to have contributed to our results. Unfortunately, our interpretations remain speculative as we could not measure the antioxidant response to exercise before and after treatment. Also, our pilot study has few other limitations: firstly, we could not randomize the participants for methodological (data on the effect of intermittent hypoxia–hyperoxia training on healthy athletes' performance are not yet available, so it was impossible for us to calculate the sample size to support a methodologically sound and clinically meaningful RCT) and logistical reasons(both the actual treatment and a 'sham IHHT' were considered by coaches too time consuming and disruptive to be embedded into the very strict training schedule of HA); secondly, we could not support our findings with measures of blood biochemistry parameters and with objective measures of OTS athletes' psychological readiness to 'return to play', these limitations being relevant due to the multifactorial nature of the syndrome; thirdly, we did not follow up the OTS group athletes to ascertain whether their maximal exercise capacity at the end of the season was similar to the one measured in HA; and lastly, OTS and HA groups were not gender balanced, these limitations potentially affecting data on performance.

As a positive note, it has to be pointed out that OTS athletes' adherence to the protocol was excellent (all those recruited completed the programme) despite each scheduled session lasting between 2 and 2·5 h.

In conclusion, our study suggest that a newly developed 4-week programme including repeated hypoxic–hyperoxic exposures combined with low-intensity sport-specific exercise improves physical working capacity, ANS balance and tolerance to hypoxia in athletes with OTS, so making this new approach a viable and useful additional tool to treat a clinical condition usually perceived by athletes as a threat to their careers. Considering the usually busy schedule of top athletes, this new method is very attractive as it helps to recover in 4 weeks of time and for this reason, future research should evaluate its effectiveness in well-conducted randomized control trials. Also, future research should focus on further investigating the mechanisms behind such a promising adaptive response as well as clarifying the role of oxidative stress/antioxidant capacity in the pathophysiology of OTS and the potential role of repeated hypoxia–hyperoxia exposure in protecting athletes from developing this bewildering syndrome.

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Conflict of interest

Dr. Davide Susta and Dr. Elena Dudnik have no financial or other interest in the product or distributor of the product. Prof. Oleg Glazachev has a consulting agreement (software design and development) with the supplier of the equipment, and he has no financial interest linked to sales or company performance. The company supplied at cost the advanced prototype used in our study.

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