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Section II - Exercise Physiology & Sports Medicine

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Acute Hormonal Responses to High-Intensity Interval Training in Hyperoxia

by

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This study aimed to compare selected hormonal responses to a single session of high intensity interval training performed with an increased fraction of inspired oxygen (hyperoxia) and under normoxic conditions. Twelve recreationally trained men (age 24 ± 3 years) performed two sessions of high intensity interval training on a cycle ergometer, in randomized order with hyperoxia (4 L·min^{-1} with a flowrate of 94% O_2) and normoxia. Each session consisted of 5 intervals of 3 minutes at 85% of the maximal power output, interspersed by 2 min at 40% of the maximal power output. Serum cortisol, prolactin and vascular endothelial growth factor (VEGF) were assessed both before and immediately after each high intensity interval training session. Statistically significant differences in cortisol were found between hyperoxic and normoxic conditions ($p = 0.011$), with a significant increase in hyperoxia (61.4 ± 73.2%, $p = 0.013$, ES = -1.03), but not in normoxia (-1.3 ± 33.5%, $p > 0.05$, ES = 0.1). Prolactin increased similarly in both hyperoxia (118.1 ± 145.1%, $p = 0.019$, ES = -0.99) and normoxia (62.14 ± 75.43%, $p = 0.005$, ES = -0.5). VEGF was not statistically altered in either of the conditions. Our findings indicate that a single session of high intensity interval training in low-dose hyperoxia significantly increased cortisol concentrations in recreationally trained individuals compared to normoxia, while the difference was smaller in prolactin and diminished in VEGF concentrations.

Key words: *HIIT, F_iO_2, hormones, Cortisol, VEGF.*

Introduction

Hyperoxia is typically defined as an increased partial pressure of intra-alveolar oxygen compared to normal breathing conditions (i.e. FiO_2 = 21%) (Cardinale and Ekblom, 2018; Llitjos et al., 2016). Numerous studies have shown acute improvements in physical performance when F_iO_2 was increased above 21% (Cardinale and Ekblom, 2018; Sperlich et al., 2017). For example, acute elevations in F_iO_2 have been associated with increased time to exhaustion during treadmill running (Wilson and Welch, 1975), higher absolute submaximal or maximal power output during stationary cycling (Knight et al., 1993; Plet et al., 1992) and lower blood lactate concentrations during exercise on a cycle ergometer (Linossier et al., 2000; Plet et al., 1992; Prieur et al., 2002). Therefore, hyperoxia provides a promising approach for athletes to use in training regimens as a mean to perform greater workloads and, hence, acutely induce a greater overload stimulus.

Physiological mechanisms underlying hyperoxia-induced acute improvements in aerobic exercise performance are yet to be elucidated, but are likely linked to improved oxygen perfusion to tissue and reduced central fatigue (Amann et al.,

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2006; Cardinale and Ekblom, 2018; Sperlich et al., 2017). In this context, endocrine mechanisms also need to be considered because changes in tissue oxygen partial pressure and oxygen availability are important regulators of hormonal release via endocrine tissues and the central nervous system (Hesse et al., 1981). In turn, evidence suggests that hormones are widely involved in a variety of exercise-induced acute physiological alterations and chronic adaptations, thus leading to improved physical performance (Hackney and Lane, 2015; Hill et al., 2008).

Along this line of reasoning, the hormone cortisol is critical to training adaptations. It acts as a key regulator of exercise metabolism by inducing gluconeogenesis and increasing free amino acid availability, with this latter action being critical to the exercise recovery/adaptation process (Hill et al., 2008; Viru and Viru, 2004). Furthermore, prolactin is suspected of playing a crucial role in activating the immune response following exercise, thus serving as a mediator to the post-exercise inflammatory processes and, thereby, also regulating the physiological adaptations to exercise training (Hackney, 2008). Finally, because main forms of aerobic exercise are strongly dependent on oxygen transport and availability (Bassett and Howley, 2000), elevations in concentrations of the vascular endothelial growth factor (VEGF) during and after strenuous exercise can be associated with improved vascular functioning and angiogenesis and, therefore, enhanced oxygen transport capacity, which is a major training adaptive response (Vital et al., 2014).

However, to the best of our knowledge, acute responses of these hormones to intensive exercise under hyperoxic conditions have rarely been studied. Over 20 years ago, Strüder et al. (1996) did report that hyperoxia resulted in a 400% increase in blood prolactin concentrations during 30 minutes of rest (i.e., prior to exercise), while during subsequent 60 minutes of stationary cycling at sub-maximal intensity, concentrations of prolactin decreased, but remained higher than under normoxic conditions. Furthermore, Brinkmann et al. (2017) showed significant increases in the VEGF, induced by 40 minutes of cycling at sub-maximal intensities with intermittent periods of hypoxia and hyperoxia in Type 2 diabetic patients. In this study, however, it is likely that the observed changes in the VEGF were induced by hypoxia rather than hyperoxia, as was previously shown in patients with Type 1 diabetes (Hall et al., 2018).

Considering the limited data on hormonal responses to intensive exercise performed under hyperoxic conditions, we aimed to investigate the cortisol, prolactin and VEGF responses to a single session of high-intensity interval training (HIIT) performed with increased F_iO_2 (hyperoxia) compared to a normoxic condition, in recreationally trained men.

Methods

Participants and ethical considerations

Twelve recreationally-trained men (age, 24 ± 3 years; body height, 184.9 ± 5.8 cm; body mass, 78.1 ± 9.6 kg) were recruited to participate in this study. Due to the novel study design and unknown effect sizes, we were not able to define the sample size as *A Priory*. However, the overall number of included participants was well in line with previous studies investigating hormonal responses to strenuous exercise (De Meirleir et al., 1985; Hackney, 2008; Kraus et al., 2004; Wahl et al., 2014, 2011) and as such was deemed sufficient. Participants were moderately physically active, as characterized by a range of exercise modes (e.g., running, cycling, or team-based sports), at light-to-moderate intensity and duration. Participants were informed about possible risks of all study procedures before providing written informed consent. All participants were non-smokers and abstained from vigorous activity, alcohol or caffeine intake over one day prior each measurement. A completed health questionnaire and resting ECG were reviewed by a cardiologist before the first exercise test. All participants were free of acute and chronic illness, disease and injury, and did not report the use of any medication that would contraindicate intense physical activity or interfere with endocrine function. The study was conducted according to the Declaration of Helsinki, and ethical approval was granted by the Ethics Committee of the German Sport University.

Study design

This study used a randomized, crossover design. After pre-screening and initial aerobic performance testing, all participants performed a single session of HIIT at a pre-determined

intensity, both under hyperoxia and normoxia in randomized order. To ensure sufficient recovery, all tests were separated by at least 48 hours of rest. Antecubital blood was drawn from participants on the day of the maximal aerobic test, as well as both before and immediately after each training session to assess for hormonal responses (cortisol, prolactin and VEGF). In addition, capillary blood samples were collected at rest as well as before and after each high-intensity bout to assess blood lactate concentrations.

HIIT sessions

The training intensities were determined by the percentage of peak power (W_{max}) obtained during the initial aerobic performance test at baseline (see the following section). Each HIIT protocol consisted of 5 intervals of 3 minutes at 85% of W_{max}, separated by 2 minutes at 40% of W_{max}. Participants were instructed to maintain a constant pedaling frequency of approximately 70 revolutions per minute during each exercise session. Hyperoxia was supplied by a generator with a flow of 4 $L \cdot min^{-1}$ with 94% O_2 (HYPOXcontrol, Medicap Homecare GmbH, Ulrichstein, Germany). The gas mixture was delivered through a full-faced respiration mask, where it was further mixed with ambient air. Normoxia was performed under ambient conditions involving room air.

Measurements of aerobic performance

Participants' W_{max} and peak oxygen uptake ($\dot{V}O_{2peak}$) were determined by an incremental protocol on a bike ergometer (Excalibur Sport, Lode BV, Groningen, the Netherlands). Because hyperoxia may lead to improved maximal performance (Cardinale and Ekblom, 2018; Sperlich et al., 2017), power output used during HIIT sessions would have been different for hyperoxia and normoxia as well. Consequently, the incremental bike ergometer test was performed only under normoxia.

The initial load for all participants was 30 Watts and was increased by 40 Watts every 3 minutes. Participants were asked to maintain a pedaling frequency of 70 rpm throughout the test. The test was terminated when participants failed to maintain the required pedaling frequency for more than 15 s, despite verbal encouragement. The heart rate was monitored throughout the protocol (Polar A300; Polar Electro Oy, Kempele, Finland) and recorded as the average of the last 5 seconds at each load. Oxygen uptake was determined continuously breath-by-breath using a gas analyzer (Zan600, Zan Messgeräte, nSpire Health GmbH, Oberthulba, Germany). On each testing day, air flow calibration was performed using a manual flow calibrator. $\dot{V}O_{2peak}$ was calculated as the highest $\dot{V}O_2$ value averaged over 30 seconds. In addition, W_{max} was determined using the following equation (Kuipers et al., 1985): $W_{max} = W_{com} + 40 \cdot (t/180)$, where W_{com} was the load of the last completed stage, 40 was power output difference between each workload, t was the time of the last incomplete stage (in seconds) and 180 was the duration of each completed workload (in seconds). This value was used to calculate the intensity for the HIIT sessions performed under both hyperoxia and normoxia.

Blood sampling and analysis

Venous blood samples were drawn to determine concentrations of cortisol, prolactin and VEGF. In order to verify normal hormonal function, fasting concentrations of these hormones were assessed on the day of the incremental bike ergometer test between 7:00 and 9:00 AM. In addition, hormonal concentrations were assessed prior to and immediately after the HIIT sessions both under hyperoxia and normoxia. Fasting values for the VEGF were above the normal range due to two outliers. However, since baseline concentrations assessed in these participants were similar also during pre-HIIT testing, it was decided to include these participants in the final analysis.

Samples were drawn by a laboratory technician from the antecubital vein into serum tubes (BD Vacutainer, BD, Heidelberg, Germany). After storage at room temperature for ~15 minutes, blood samples were centrifuged at 3000 rpm for 10 minutes. The serum was then stored at -80°C until analysis. Enzyme-linked immunosorbent assay (ELISA) kits from DRG Instruments GmbH (Marburg, Germany) were used to quantify the serum hormone concentrations: Cortisol (EIA-1887), Prolactin (EIA-1291), and VEGF-A (EIA-4826). All measurements were performed in duplicate and the individual mean values were used for further analyses. Sensitivities for cortisol, prolactin, and VEGF were 2.5 $ng \cdot mL^{-1}$, 0.35 $ng \cdot mL^{-1}$ and 7.9 $pg \cdot mL^{-1}$, respectively. Intra-assay coefficients of variation for cortisol, prolactin, and VEGF were

5.6%, 4.5% and 6.2%, respectively. Inter-assay coefficients of variation for Cortisol, Prolactin, and VEGF were 6.9%, 5.9% and 4.3%, respectively. Blood lactate concentrations were determined at rest as well as before and after each high-intensity bout. Capillary blood samples (20 μl) were collected from the earlobe and mixed with a hemolytic fluid. Thereafter, blood lactate concentrations were assessed using a fully enzymatic amperometric instrument (EKF Biosen S-Line Analyzer, Diagnostic, GmbH, Barleben, Germany).

Statistical analysis

Data are expressed as mean ± SD and were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 21.0 (Chicago, IL, USA). Prior to statistical analysis, data were checked for normality using the Shapiro-Wilk test. To avoid non-uniformity bias, hormonal data were log transformed. All data were analyzed by a two-way (condition x time) repeated measures analysis of variance (ANOVA) with Bonferroni corrections. Significance for all tests was defined as $p \leq 0.05$, while *p-values* < 0.1 were accepted as a significant trend. Effect sizes (*ES*) were calculated using the formula $ES = t_c[2(1-r)/n]^{1/2}$ proposed by Dunlap et al. (1996), where t_c was the t-score, r was the correlation, and n was the number of participants considered. Associations between exercise-induced changes in serum hormone concentrations and blood lactate concentrations were examined using Spearman's Rank correlation.

Results

Participants' characteristics

Participants' physical characteristics and fasting hormonal concentrations are presented in Table 1.

Cortisol

A statistically significant main effect was observed for time ($p = 0.054$, $F = 4.154$) and for time X condition ($p = 0.010$, $F = 7.863$) (Figure 1). Within-condition analysis revealed that cortisol significantly increased only under hyperoxia (by 61.4 ± 73.2%, $p = 0.013$, *ES* = -1.03), while it was statistically unchanged under normoxia (-1.3 ± 33.5%, $p = 0.519$, *ES* = 0.1). Furthermore, change under hyperoxia was significantly larger than that observed under normoxia ($p = 0.011$).

Prolactin

A statistically significant main effect for time ($p < 0.001$, $F = 20.054$), but not for time X condition ($p = 0.315$, $F = 1.058$), was observed for serum prolactin concentrations (Figure 2). Specifically, prolactin significantly increased similarly under both hyperoxic (118.1 ± 145.2%, $p = 0.019$, *ES* = -0.99) and normoxic (62.1 ± 75.4%, $p = 0.005$, *ES* = -0.5) conditions.

VEGF

No statistically significant main effect for time ($p = 0.238$, $F = 1.471$) or time X condition ($p = 0.320$, $F = 1,037$) was observed for serum VEGF concentrations (Figure 3).

Blood lactate concentrations

A statistically main effect for time ($p < 0.001$, $F = 178.3$), but not for time X condition ($p = 0.230$, $F = 1.530$), was found for blood lactate concentrations. Blood lactate concentrations significantly increased under both hyperoxia (by 7.45-fold, $p < 0.001$, *ES* = 3.2) and normoxia (by 8.17-fold, $p < 0.001$, *ES* = 4.7).

Correlations

The relative changes in blood lactate concentrations were associated with changes in prolactin and cortisol only under hyperoxia ($r = 0.594$, $p = 0.042$ and r = 0.664, $p = 0.018$), but not under normoxia.

Discussion

The purpose of this study was to assess the acute effects of HIIT performed under hyperoxia and normoxia on hormonal responses in recreationally trained individuals. We found a significant increase in serum cortisol concentrations only following HIIT under hyperoxia, while changes in prolactin and the VEGF did not statistically differ during exercise between the hyperoxic and normoxic conditions.

Previous studies have indicated that physical exercise can have powerful acute effects on hormonal release (Galbo, 1983; Hackney and Lane, 2015). In this regard, exercise-induced increases in blood cortisol (Galbo, 1983), prolactin (Hackney, 2008; Rojas Vega et al., 2012), and VEGF (Kadi, 2005) levels have been well documented. Interestingly, in the present study, statistically significant increases in cortisol concentrations were only observed in the group performing HIIT under hyperoxia.

Table 1

Participants' physical characteristics as well as baseline performance and hormonal concentrations

Characteristic	Mean ± SD
Age (years)	24 ± 3
Body height (cm)	184.9 ± 5.8
Body mass (kg)	78.1 ± 9.6
Body mass Index ($kg \cdot m^{-2}$)	22.8 ± 1.8
Body fat (%)	13.9 ± 1.9
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	53.8 ± 5.2
Maximal Aerobic Power (W)	309 ± 37
VEGF ($pg \cdot mL^{-1}$)	474.3 ± 312.5
Prolactin ($ng \cdot mL^{-1}$)	8.1 ± 4.2
Cortisol ($ng \cdot mL^{-1}$)	235.0 ± 52.6

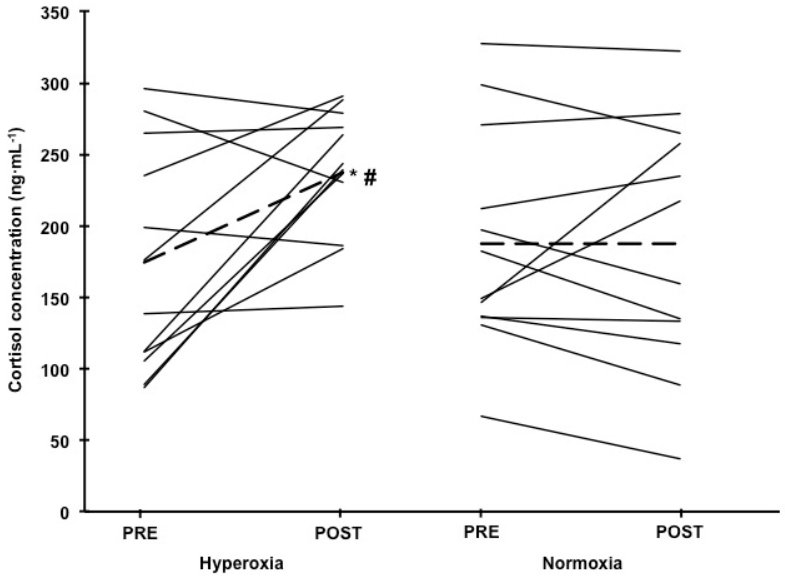

Figure 1

*Serum cortisol concentrations before and after the HIIT session under hyperoxia and normoxia. * $p \leq 0.05$ from pre to post loading, # $p \leq 0.05$ between groups post loading*

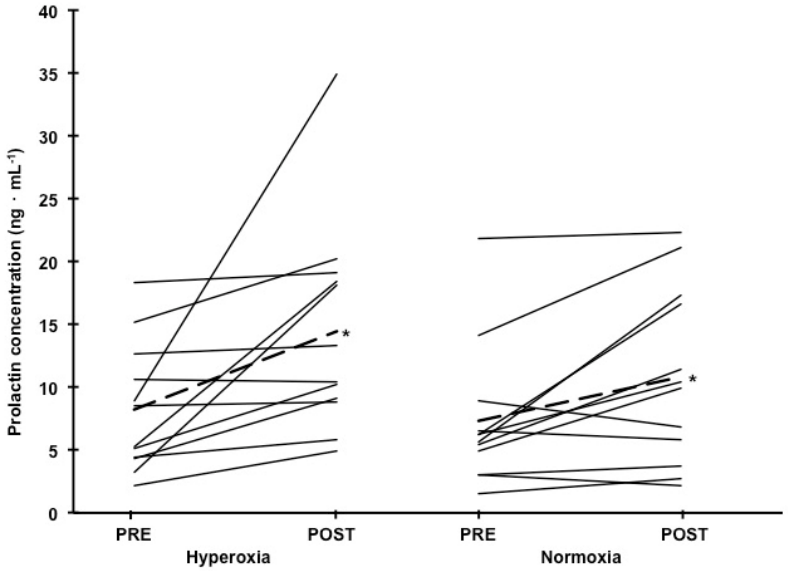

Figure 2

*Serum prolactin concentrations before and after the HIIT session under hyperoxia and normoxia. * $p \leq 0.054$ from pre to post loading*

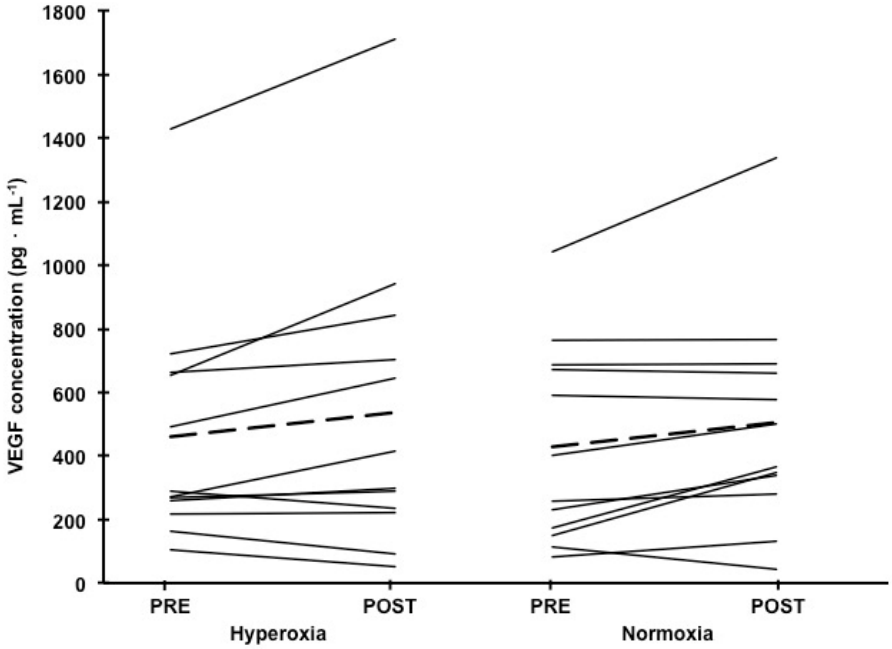

Figure 3

Serum VEGF concentrations before and after the HIIT session under hyperoxia and normoxia.

This finding was somewhat surprising, considering that increased FiO_2 may counteract exercise-induced local ischemia (Bannister and Cunningham, 1954; Cardinale and Ekblom, 2018; Sperlich et al., 2017) and, thus, presumably lead to lower physical strain, likely reflected in lower cortisol responses (Hackney, 2008). In fact, this hypothesis was somewhat confirmed by the significant correlation between the changes in cortisol concentration and blood lactate accumulation, indicating that cortisol responses were highest in those subjects with higher increases in blood lactate.

One suggestion to explain the augmented cortisol response under hyperoxia is related to the increased formation of reactive oxygen species (ROS), typically observed with increased oxygen availability (Turrens, 2003). In fact, it was previously shown *in vitro* that ROS diminished, or even abolished the negative feedback regulation of glucocorticoids (Asaba et al., 2004), which in turn would lead to increased circulating levels of cortisol. To the best of our knowledge, this is the first evidence *in vivo* suggesting that already mild hyperoxic conditions (4 $L \cdot min^{-1}$ with 94% O_2) may also be one of the factors influencing the regulation of the hypothalamic-pituitary-adrenal axis and, therefore, cortisol release. However, since ROS was not assessed in the present study, this theory requires further investigation.

We did not observe changes in cortisol concentrations when HIIT was performed under normoxia. These results are in contrast to previous findings, which typically report significant increases in cortisol immediately following strenuous aerobic exercise (Galbo, 1983; Hill et al., 2008). According to the theory reported by Galbo et al. (1983) and Hill et al. (2008), cortisol increases at intensities above 50 - 60% of $\dot{V}O_{2max}$, while it decreases at workloads below 50% of $\dot{V}O_{2max}$. Since the present HIIT consisted of 5 intervals of 3 minutes at 85% of W_{max} interspersed by 2 minutes at 40% of W_{max}, it might be suggested that cortisol increased during the final 3 minutes performed at high-intensity, but this increase was followed by an augmented removal rate during the subsequent recovery. However, this explanation is not supported by a previous investigation which showed that circulating cortisol significantly increased during strenuous exercise despite an active recovery of 3 minutes (Wahl et al., 2014). It is also possible that the peak of cortisol concentrations may have occurred later into the recovery period as was shown previously (Daly et al., 2005), providing a procedural limitation of the present study in which hormonal concentrations were assessed only once following the loading. The contradictory findings within our cortisol outcomes presently cannot be explained and are in need of further research work.

Another interesting finding of this study was that prolactin significantly increased to a similar extent under both hyperoxia and normoxia. However, the effect size differences suggest the increase to be larger under hyperoxic conditions compared to normoxia. Moreover, a significant correlation was observed between changes in blood lactate concentrations and prolactin only under the hyperoxic condition. Changes of prolactin may be of interest because of its multiple regulatory effects on reproduction, homeostasis, growth and development as well as immunoregulation, all of which are essential components of physiological and morphological training adaptations (Hackney et al., 2016; Rojas Vega et al., 2012). Prolactin seems to be released in response to various forms of stress, including, but not limited to, exercise (Strüder et al., 1996). Furthermore, numerous studies have shown that prolactin commences to rise when a minimum intensity of 70% of $\dot{V}O_{2max}$ is achieved (Lüger et al., 1992; Rojas Vega et al., 2012). Therefore, any changes are unlikely to occur at intensities below the lactate threshold (De Meirleir et al., 1985; Hackney et al., 2016). This assumption is partially supported in the present study, where a small positive correlation was found between the increases in prolactin and blood lactate concentrations under both hyperoxia and normoxia.

Exercise-induced prolactin responses do seem to be related to oxygen availability. That is, Strüder at al. (1996) reported augmented levels of prolactin during breathing under hyperoxia (100% O_2), compared to hypoxia (14% O_2) or normoxia (Strüder et al., 1996). Contrastingly, Bouissou et al. (1987) reported that acute hypoxia (14.5% O_2) may inhibit prolactin response to exercise. Our findings of a somewhat larger increase in prolactin concentrations under hyperoxia compared to normoxia, thus, indicate that even a small increase in FiO_2 may already

counteract possible hypoxic effects of strenuous exercise, as has previously been demonstrated by studies showing improved oxygenation under hyperoxic conditions (Sperlich et al., 2017).

It is well established that strenuous exercise elicits acute and chronic increases in intra-muscular and circulating VEGF levels (Kadi, 2005; Kraus et al., 2004; Wahl et al., 2011). However, our findings for the VEGF are difficult to interpret. In line with previous findings (Kraus et al., 2004), we showed a considerable variation of serum VEGF concentrations between individuals (6.8 ± 31.7% under hyperoxia and 29.7 ± 52.3% under normoxia). While the percentage changes suggests a larger increase under normoxia, neither the *p*-value nor the effect sizes support this interpretation. On the one hand, this lack of significance may be due to the high individual response variability in our participants, rather than to technical error within our biochemical analysis. On the other hand, the statistically similar changes in the VEGF may also be related to similar blood lactate concentrations under the two conditions. This is because at least in rodents it was previously shown that cerebral VEGF release was triggered by activation of the lactate receptor HCAR1 (Morland et al., 2017). Interestingly, in Type 2 diabetic patients a significantly larger increase in VEGF concentrations was observed already after sub-maximal endurance cycling when subjects were breathing intermittent hypoxic (14% O_2) and hyperoxic (30% O_2) air as compared to normoxic conditions (Brinkmann et al., 2017), but it is likely that this was induced by hypoxia rather than hyperoxia (Hall et al., 2018). Future research therefore needs to address our observed anomaly and discern whether our findings are real or an artifact.

In conclusion, the present study indicated that HIIT performed under low hyperoxia may induce statistically larger increases in cortisol concentrations as compared to normoxic conditions, while a slight increase in the ambient oxygen availability may only have small effects on changes in prolactin and negligible effects on changes in the VEGF. From a practical point of view we, therefore, suggest that higher concentrations of supplemental oxygen may be administered in order to optimize the hormonal responses to strenuous exercise and, thus, induce beneficial biological adaptations.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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