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The Effect of Intermittent Hypoxia Training on Hematological Parameters in Sprague Dawley Rats: A Randomized Control Trial

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Abstract

Background: Intermittent hypoxia training has been proposed as a potent facilitator of hematological adaptability, especially with respect to red blood cell proliferation and hemoglobin concentration. However, the comprehensive physiological implications of intermittent hypoxia training, as compared to normoxia training and intermittent hypoxia exposure, remain incompletely understood.

Methods: Ninety Sprague Dawley rats were randomly allocated into three experimental groups: intermittent hypoxia training, normoxia training, and intermittent hypoxia exposure, each consisting of 30 rats further stratified by gender. Hematological parameters, including hemoglobin level, red blood cell count, and hematocrit value, were evaluated at 24-hour intervals post the culmination of each training week for a span of 12 weeks. The study employed repeated measures analysis of variance to compare variations in these metrics across the experimental groups.

Results: Longitudinal assessment revealed a consistent uptrend in hemoglobin level, red blood cell count, and hematocrit value across all groups. However, the Sprague Dawley rats of intermittent hypoxia training group exhibited the most pronounced elevation in these parameters. A statistically significant elevation was observed in the intermittent hypoxia training group relative to both the intermittent hypoxia exposure and normoxia training groups starting from the seventh and eighth weeks, respectively.

Conclusion: Our findings confirmed the superior facilitative impact of intermittent hypoxia training on hematological parameters related to hemoglobin level, red blood cell count, and hematocrit value. These results contribute significantly to the extant body of knowledge concerning the intricate adaptive physiological mechanisms orchestrated under conditions of intermittent hypoxia and aerobic exercise. Furthermore, the data generated from this investigation serve as a robust foundational platform for future scholarly endeavors that aim to leverage these identified mechanisms for potential therapeutic applications.

Introduction

The concept of altitude or hypoxic training is a common practice for improving aerobic capacity and endurance performance (Czuba et al., 2013) . Several strategies of altitude training, like “live high + train high”, “live high + train low” and “live low + train high” have been proposed (CWilber, 2007; Bonne et al., 2014; Girard et al., 2023; Hauser et al., 2017; Çolak et al., 2021; Hauser et al., 2018; Stray-Gundersen et al., 2001; Brugniaux et al., 2006; Wehrlin et al., 2006; Girard et al., 2020). They are based on adaptive changes of humans to chronic hypoxia (Levine and Stray-Gundersen, 1997). Chronic exposure to altitude improves oxygen transport capacity by enhancing erythropoietin (EPO)

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secretion (Jelkmann, 1992), hemoglobin mass (Moore, 2017) and maximal oxygen uptake (VO_2 max) (Girard et al., 2020) thus promotes exercise performance (Czuba et al., 2013). However, not all athletes or teams have the resources to travel to high altitude environments on a regular basis. During the last years several strategies, such as the intermittent hypoxia training (IHT), have been used to increase the athletes' sea level performance (Millet et al., 2010; Ambroży et al., 2020; Nimje et al., 2020; Hendriksen and Meeuwsen, 2003; Morton and Cable, 2005; Ramos-Campo et al., 2015; Roels et al., 2007; Hinghofer-Szalkay, 2010; Lippi and Franchini, 2010; Sanchez and Borrani, 2018). IHT refers to the discontinuous use of normobaric or hypobaric hypoxia, in an attempt to reproduce some of these key features of altitude acclimatization, with the ultimate goal to improve sea-level athletic performance (Levine, 2002). In this method, athletes live in normoxic conditions and train in hypoxic environment (Millet et al., 2010).In the realm of altitude training, IHT emerges as a pivotal strategy, addressing the limitations inherent in traditional altitude training methods. Moreover, it stands as an instrumental technique to augment the athletic prowess of elite competitors. Within the intricate physiological tapestry of the human body, blood serves as a fundamental conduit, orchestrating the equilibrium and numeration of diverse cellular constituents within. The vitality and equilibrium of blood cells play an indispensable role in upholding the immune functionality (Dobkin and Mangalmurti, 2022), facilitating oxygen transference (Hamasaki and Yamamoto, 2000), and maintaining metabolic homeostasis (Starostová et al., 2013). Nevertheless, the existing body of research examining the ramifications of IHT on hematological parameters, especially in mammalian experimental studies, remains somewhat in its nascent stages. In light of this gap, the current investigation endeavors to delve into the repercussions of IHT on the hematological metrics of rodent subjects. By harnessing the rigor of randomized controlled trial and assessing hematological parameters [encompassing hemoglobin (HGB), red blood cell (RBC), and hematocrit (HCT)] within Sprague Dawley (SD) rats, this study aims to elucidate the intricate biochemical and physiological mechanisms through which Intermittent Hypoxic Training (IHT) modulates hematological parameters, in comparison to Normoxia Training (NT) and Intermittent Hypoxia Exposure (IHE). The findings will hopefully illuminate the prospective utility of IHT, furnishing a robust academic foundation for ensuing dialogues centered on its potential to amplify athletic competence and other related domains.

Materials and methods

Experimental subjects:

For the purpose of this study, we recruited a cohort of 90 SD rats, each approximately two months of age. At the onset of the study, these specimens displayed an average body mass of 138.27 ± 5.839 g. Throughout a preliminary two-week acclimatization phase, stringent controls were imposed upon the environmental parameters within the designated housing facility. Ambient temperatures were diligently regulated at 23±3 °C, while ensuring that the relative humidity hovered around 50 ± 5% consistently. The photoperiod was meticulously set to mirror a 12-hour light/12-hour dark cycle. Prioritizing the holistic welfare of the SD rats, the housing chamber was equipped with efficient ventilation systems. To further cater to their cognitive needs and avert potential behavioral aberrations, an assortment of toys and stimuli was judiciously placed within their habitat. Nutritionally balanced feed and untainted water were dispensed at regular intervals. The maintenance regime included expedited removal of residual food and fecal matter, fortifying the hygiene and sanitation of the facility. To monitor their health trajectory, the SD rats underwent routine health evaluations, with the deployment of both prophylactic and therapeutic interventions when deemed essential. Subsequent to the acclimatization span, there was a notable augmentation in the SD rats' body mass, registering at 187.74 ± 9.69 g. Such meticulous preparatory and maintenance protocols underscore our commitment to upholding the credibility and methodological integrity of the study. All protocols of animal experiments complied with Animal Research: Reporting of In Vivo Experiments Guidelines (Percie du Sert et al., 2020). This study was approved by the Ethics Committee of Shandong Institute of Petroleum and Chemical Technology (registered number: KY-2023-033).

Experimental groups design:

Utilizing a randomized number table method, the 90 SD rats were arbitrarily divided into three distinct groups, each consisting of 30 individuals, further stratified by gender with 15 males and 15 females in each. We employed a hypoxia device to create an appropriate hypoxic environment and utilized an oxygen concentration meter for accurate oxygen content measurements.

IHT group:

The preliminary week was dedicated to acclimatization, during which SD rats were introduced to a hypoxic milieu characterized by an oxygen volume fraction of 15%. Over subsequent weeks, a systematic decrement in this fraction was instituted, culminating in a reduction from the initial 15% to a final concentration of 10%. Training paradigms consisted of rigorous 15-minute aerobic sessions under hypoxic constraints, interspersed with five-minute recuperative intervals, aggregating to a daily total of 1.5 hours. This regimen was consistently maintained over a span of 12 weeks, demarcated by five active days followed

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by a rest phase of two days.

NT group:

SD rats in this assembly were domiciled under normobaric parameters. Training paradigms consisted of rigorous 15-minute aerobic sessions, interspersed with five-minute recuperative intervals, aggregating to a daily total of 1.5 hours. This regimen was consistently maintained over a span of 12 weeks, demarcated by five active days followed by a rest phase of two days.

IHE group:

The preliminary week was dedicated to acclimatization, during which SD rats were introduced to a hypoxic milieu characterized by an oxygen volume fraction of 15%. Over subsequent weeks, a systematic decrement in this fraction was instituted, culminating in a reduction from the initial 15% to a final concentration of 10%. The daily engagement involved 15 minutes of exposure to the hypoxic conditions, interspaced by five-minute intervals, cumulatively accounting for 1.5 hours. This regimen was consistently maintained over a span of 12 weeks, demarcated by five active days followed by a rest phase of two days.

Hematological evaluation:

Prior to the initiation of the experiment and at 24-hour intervals post the culmination of each training week, blood specimens were meticulously extracted from the jugular vein. These samples were then subjected to detailed hematological assessments using a sophisticated animal blood analyzer. The metrics under evaluation included HGB level, RBC Count, and HCT value.

Statistical analysis:

Data analysis was conducted using SPSS version 27.0. Quantitative data were presented as mean ± standard deviation. Repeated measures analysis of variance (ANOVA) was utilized to compare the variations in HGB level, RBC Count, and HTC value across different groups over the duration of the experiment. The level of significance was set at P=0.05.

Results

Influence of different experiments on HGB level in SD rats:

Prior to the commencement of the experimental procedures, one-way ANOVA confirmed that there were no statistically significant variations in the baseline HGB level across the three experimental SD rat groups (P > 0.05). As the longitudinal study advanced, a discernible uptrend in HGB level was observed in all groups, culminating in a stabilization phase post the 10-week mark. Remarkably, the IHT group manifested the most pronounced elevation in HGB level. Beginning from the seventh week, a statistically significant elevation was recorded in the IHT group when compared to the IHE group. This difference became significant compared to the NT group as well, commencing from the eighth week. (Supplemental table 1, Supplemental table 2, Supplemental table 3, Supplemental table 4, Figure 1)

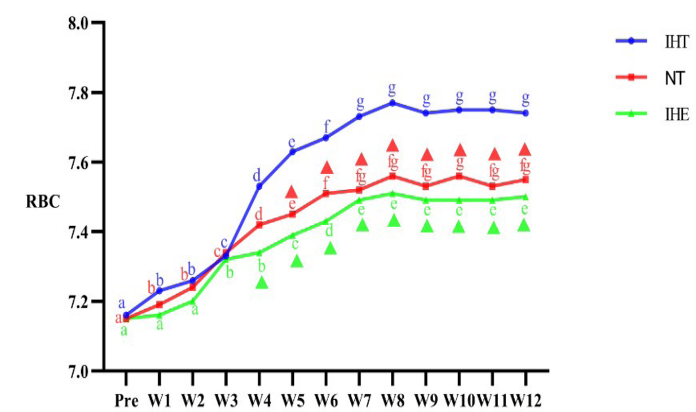

Figure 1: *The comparison of HB changes in rats after 12-week training. Note: The letters "abcdefgh" indicate the time point differences using the letter marking method (intra-group comparison); the symbol "△" indicates significant differences compared to IHT group (inter-group comparison).*

Supplemental table 1: *Original data (HB)*

Supplementary Table 1

Supplemental table 2: *scriptive statistics (HB)*

Supplementary Table 2

Supplemental table 3: *Paired comparison of time (HB)*

Supplementary Table 3

Supplemental table 4: *Paired comparison of groups (HB)*

Supplementary Table 4

Influence of different experiments on RBC count in SD rats:

Prior to the commencement of the experimental procedures, one-way ANOVA confirmed that there were no statistically significant variations in the baseline RBC count across the three experimental SD rat groups (P > 0.05). As the longitudinal study advanced, a discernible uptrend in RBC count was observed in all groups, culminating in a stabilization phase post the seven-week mark. Remarkably, the IHT group manifested the most pronounced elevation in RBC count. Beginning from the fourth week, a statistically significant elevation was recorded in the IHT group when compared to the IHE group. This difference became significant compared to the NT group as well, commencing from the fifth week. (Supplemental table 5, Supplemental

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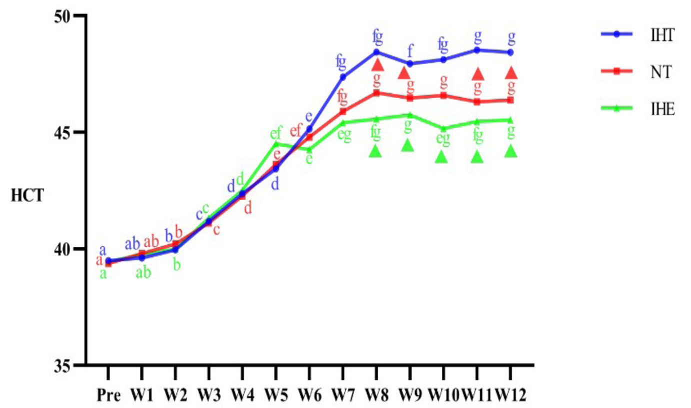

Figure 2: The comparison of RBC changes in rats after 12-week training. Note: The letters "abcdefg" indicate the time point differences using the letter marking method (intra-group comparison); the symbol "△" indicates significant differences compared to IHT group (inter-group comparison).

Supplemental table 5: *Original data (RBC)*

Supplementary Table 5

Supplemental table 6: *Descriptive statistics (RBC)*

Supplementary Table 6

Supplemental table 7: *Paired comparison of time (RBC)*

Supplementary Table 7

Supplemental table 8: *Paired comparison of groups (RBC)*

Supplementary Table 8

table 6, Supplemental table 7, Supplemental table 8, Figure 2)

Influence of different experiments on HCT value in SD rats:

Prior to the commencement of the experimental procedures, one-way ANOVA confirmed that there were no statistically significant variations in the baseline HCT value across the three experimental SD rat groups (P > 0.05). As the longitudinal study advanced, a discernible uptrend in HCT value was observed in all groups, culminating in a stabilization phase post the 10-week mark for IHT group, seven-week mark for NI group and IHE group. Remarkably, the IHT group manifested the most pronounced elevation in HCT value. Beginning from the eighth week, a statistically significant elevation was recorded in the IHT group when compared to the IHE group. This difference

Supplemental table 9: *Original data (HCT)*

Supplementary Table 9

Supplemental table 10: *Descriptive statistics (HCT)*

Supplementary Table 10

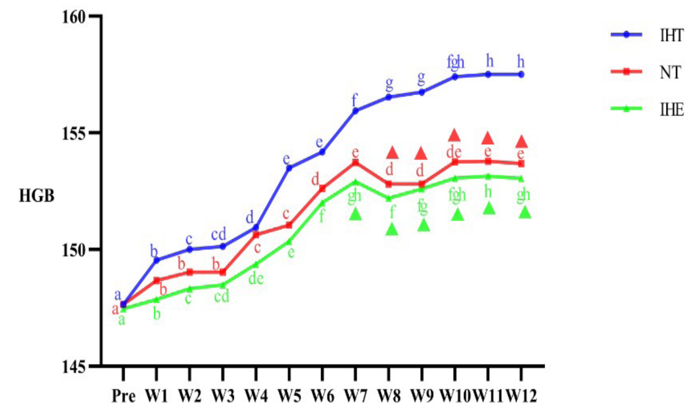

Figure 3: The comparison of HCT changes in rats after 12-week training. Note: The letters "abcdefg" indicate the time point differences using the letter marking method (intra-group comparison); the symbol "△" indicates significant differences compared to IHT group (inter-group comparison).

Supplemental table 11: *Paired comparison of time (HCT)*

Supplementary Table 11

Supplemental table 12: *Paired comparison of groups (HCT)*

Supplementary Table 12

became significant compared to the NT group as well, for the eighth, ninth, 11th, and 12th week. (Supplemental table 9, Supplemental table 10, Supplemental table 11, Supplemental table 12, Figure 3)

Discussion

Following a comprehensive 12-week investigation, we conducted meticulous experimental assessments on SD rats that were subjected to three distinct experimental conditions. The objective was to scrutinize the intricate ramifications of intermittent hypoxia training on key hematological parameters, specifically HGB level, RBC Count, and HCT value.

In our initial observational data, we noted significant elevations in HGB level, RBC Count, and HCT value across all three experimental SD rats. This conspicuous alteration in physiological markers may be attributable to adaptive biological mechanisms activated under conditions of hypoxia or physical exertion. When encountering varied external environmental stressors, not only rats but also other mammals, including humans, initiate a cascade of physiological modifications to adapt to these new circumstances (Li et al., 2021; Hellsten and Nyberg, 2015). These adaptive mechanisms serve to maintain metabolic stability and essential life functions under a range of conditions. Upon exposure to hypoxic environments or during episodes of physical activity, there is a stabilization and subsequent accumulation of intracellular Hypoxia

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Inducible Factors (Baker and Parise, 2016). This triggers the activation of genes instrumental in oxygen homeostasis. Such activation facilitates the secretion of EPO from the kidneys (Ogawa et al., 2023), ensuring an adequate oxygen supply under challenging conditions. Concurrently, both hypoxic conditions and physical exertion induce the spleen to liberate its reservoir of stored RBCs (Engan et al., 2014). This mechanism provides an immediate boost to the circulating RBC mass and, consequently, the blood's oxygen-carrying capacity. Additionally, sustained periods of hypoxia or physical exercise could potentially stimulate the bone marrow to expedite the production of RBCs (Hu and Lin, 2012; Antonelli et al., 2021).

Subsequent to our comprehensive data analysis, it was unequivocally observed that SD rats subjected to IHT exhibited a superior physiological response across all evaluated hematological parameters, with this divergence becoming notably pronounced during the mid-to-late phases of our 12-week experimental timeline. This compelling outcome compellingly indicates that the IHT regimen synergistically combines two critical physiological stimuli—hypoxia and physical exercise—to create an unparalleled physiological environment for rodent subjects. In a comparative assessment, it was revealed that SD rats undergoing IHT manifested a statistically significant elevation in HGB level, RBC Count, and HCT value relative to those undergoing either IHE or NT in isolation. Ultimately, as the experiment unfolded, the heightened physiological adaptability conferred by this confluence of stimuli became increasingly manifest, resulting in hematological parameters for the IHT group SD rats that were demonstrably superior to those of control groups.

Following an exhaustive longitudinal analysis of time-series data, it was discerned that the hematological parameters in all three experimental SD rats exhibited a trend towards stabilization between the seventh and 10th weeks of the study period. This salient observation strongly suggests that a physiological plateau in RBC proliferation and HB concentration is attained following a sustained period of hypoxic exposure or aerobic activity, marked by a decelerated rate of increment for these parameters.

This intriguing phenomenon can be ascribed to a confluence of multiple, interconnected physiological mechanisms. Firstly, it is evident that with the elapse of time, SD rats manifest adaptive responses to the imposed environmental conditions, whether it be hypoxia, normoxia training, or a synergistic combination thereof. It is well-documented that as biological organisms acclimate to external stimuli, there is a concomitant attenuation in the magnitude of their physiological responses. Secondly, longitudinal data suggest that the secretion of EPO may reach a state of equilibrium, consequently retarding the rate at which RBC and HB are generated.

Thirdly, the equilibrium between erythrocyte production and senescence must be noted as an additional contributory factor. Newly generated erythrocytes increase the overall RBC count, while senescent erythrocytes are systematically phagocytosed and eliminated by the reticuloendothelial system, particularly the spleen (Duez et al., 2015). As time advances, these complementary processes may reach a dynamic balance, thereby stabilizing the overall erythrocyte population.

Lastly, it is plausible to posit that extended periods of strenuous physical activity could induce fatigue in erythropoietic tissues such as the bone marrow, culminating in a diminished efficiency of RBC production.

In conclusion, our study underscored the potent facilitative impact of IHT on hematological parameters in Sprague-Dawley rats. Nonetheless, our data also pointed to the onset of a physiological plateau following extended periods of continuous hypoxic and/or physical stimuli, manifested by a deceleration in the rate of increase for HGB level, RBC Count, and HCT value. These empirical observations contribute valuable perspectives on the adaptive physiological mechanisms employed by mammals in hypoxic conditions and/or aerobic activity, thereby offering a substantive foundation for future investigative endeavors and potential therapeutic applications.

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Author Contributions: Z.H., X.R., S.J., and W.J. devised the project and the main conceptual ideas and planned the research. Z.H., X.R., and SW worked out the methodology. Z.H., X.R., and S.J. performed the data collection. Z.H. and X.R. also organized and maintained research data for analysis. Z.H. performed analytic calculations. Z.H., X.R., and W.J. validated the reproducibility of the results. Z.H., S.J., and W.J. wrote the manuscript with input from all authors. Z.H., S.J., and S.W. extensively reviewed the work and further edited the manuscript. All authors contributed to the artiSJe and approved the submitted version.

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