New Approaches in Exercise Physiology (NAEP), Vol 4, No 7, 120-144, Sep 2022

The Effect of 2-Day Intermittent Hypoxia-Hyperoxic Training on Anaerobic Metabolism

Yi Ching Fang
Ph.D. Graduate Institute of Athletics and Coaching Science, National Taiwan Sport University, Taoyuan, Taiwan.

Jia-Tzer Jang
Assistant Professor, National Taiwan Sport University, Taoyuan, Taiwan.

Chia-Hui Chen
Assistant Professor, National Taiwan University of Science and Technology, Taipei, Taiwan.

Te-Sheng Chen*
Graduate Institute of Athletics and Coaching Science, National Taiwan Sport University, Taoyuan, Taiwan.

Yasmin Pakzad-Mayer
Graduate Institute of Athletics and Coaching Science, National Taiwan Sport University, Taoyuan, Taiwan

Peter Karl Mayer
China Medical University, Taichung, Taiwan.

Received: December 19, 2022; **Accepted:** January 27, 2023

doi: 10.22054/NASS.2023.71543.1122

Abstract

Purpose: Researchers have studied practical applications of high-intensity interval training and hypoxic training. PGC-1α, IGF-I, and HIF-1α are generated from high-intensity interval training and affect muscle cells. Altitude training also produces HIF-1α, which induces erythropoietin and increases the number of red blood cells. However, due to the limit on training intensity and cycle, it was replaced by normobaric hypoxia training. To investigate the effects of 2-day high-intensity interval training on muscular anaerobic metabolism at varying oxygen concentrations for 2 days. **Method:** Ten subjects performed 2 consecutive days of intermittent hypoxia-hyperoxic training (IHHT); intensity of training was determined by the sprint test results. IHHT comprised 4 sets of 3 repetitions for 40 seconds (4 × 3 × 40 s); the intensity and oxygen concentration were 80% of

* **Author's e-mail:** fleanna1992@gmail.com, v4.laktat@gmail.com, monkey0209@gmail.com, spdi.researcher@gmail.com **(Corresponding Author)**, ypakzad@gmx.de, piotrmayer@hotmail.com

maximal effort and 13% oxygen for the first and third sets, and were 90% of maximal effort and 21% oxygen for the second and fourth set; participants walked for 3 min wearing an oxygen mask (O2 80%) before each set. Differences in biological parameters between the two days of training was analyzed by t-test. **Results:** The difference of mean lactate levels between two days were 0.96 ± 0.75 mmol/l at Set 3 (P = .003) and 1.05 ± 1.12 mmol/l at Set 4 (P = .016), respectively. Mean ammonia concentrations at Set 4 were 117.70 ± 29.8 μmol/l for the first day and 94.50 ± 14.45 μmol/l for the second day (P = .057). The difference of heart rate were 4.20 ± 5.05 min-1 at Set 1 (P = .027) and 4.00 ± 5.48 min-1 at Set 2 (P = .046). **Conclusions:** Two-day intermittent hypoxia-hyperoxic training affected lactate and heart rate.
Keywords: Hypoxic, Lactate, Heart Rate.

INTRODUCTION

Oxygen transport capacity is critical for athletic performance (Karlsson et al., 1967) because the production of adenosine triphosphate in the body depends on the rapid transfer of oxygen from air to mitochondria in muscle and their oxygen metabolism capacity (Wagner, 2010). Severe hypoxia may cause pathological changes to organ structure and function (Michiels, 2004). As a result, when exercising in hypoxia would cause higher physiogical pressure: the need of oxygen in working muscle would lead to higher lactate production, even ammonia. Also, the heart would beat quicker in order to supply oxygen, but still not enough for working muscle. To overcome the pathological reaction caused by hypoxia during exercise, researchers have studied practical applications of high-intensity interval training (HIIT) and hypoxic training.

It has reported that HIIT can increase metabolism (Laursen & Jenkins, 2002). As a result, substantial calories can be consumed during training, and elevated fat burning can last up to 48 h. In addition, growth hormone is released to promote muscle growth and increase maximal oxygen uptake, enhance regeneration capacity, and overcome training stagnation. All of the aforementioned effects can reduce the symptoms of hypoxia. Therefore, the exercise pattern of HIIT has been studied extensively and is primarily focused on changes in muscle cells. That is, the anaerobic conversion of pyruvate to lactate, which induces muscle cell changes and the production of monocarboxylate transporter 1

(MCT1), peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), and hypoxia-inducible factor-1 alpha (HIF-1α) (Egan et al., 2010; Norrbom et al., 2004). The lactate accumulation (LA) is positively correlated with PGC-1α (Brooks et al, 2008), and is closely related to MCT1 concentration (Wahl et al., 2009). MCT1 is predominantly found in slow-twitch muscle and promotes lactate transport in skeletal muscle for the regulation of pH in muscle cells (Thomas et al., 2007).

HIF-1α is produced when the human body is hypoxic (Jelkmann, 1992), and stimulates an increase in erythropoietin and the production of red blood cells (Heinicke et al, 2002). Thus, oxygen transport to muscle cells is improved to alleviate symptoms of tissue hypoxia. In addition, Eltzschig et al. (2014) demonstrated that reduced HIF-1α content can inhibit glucose-stimulated adenosine triphosphate (ATP) production and the function of β-cells. By contrast, increased HIF-1α can improve insulin secretion and glucose tolerance. Hypoxic training at high altitudes thus became a key training method for improving endurance. However, the challenges of hypoxic training in natural high-altitude environments limit training intensity and training cycles. For example, specialized training cannot be conducted and prematch adjustments cannot be achieved. Therefore, hypoxic training in low altitudes began to replace hypoxic training in high altitudes to improve energy metabolism mechanism during muscle hypoxia, such as by increasing enzyme activity, enhancing mitochondrial metabolism, and improving the performance of fast-twitch muscles through compensatory vasodilation and faster creatine phosphate resynthesis (Brocherie et al., 2018; Faiss et al., 2013; Hoppeler, & Vogt, 2001; McDonough et al, 2005; Zoll et al., 2006; Millet et al, 2019). Cycles and timing of hypoxic training have also changed substantially. Natural hypoxic training at high altitude usually requires 2–3 weeks, whereas hypoxic stimulation at low altitudes combined with HIIT can shorten the time required to achieve training goals to 3–5 days. Moreover, Jang et al. (2012) demonstrated that anaerobic metabolism and systemic circulation can be substantially improved by the third day of hypoxic training at low altitudes.

In recent years, intermittent hypoxic–hyperoxic training (IHHT) has been developed to improve mitochondrial activity. The protective effects of adaptation to hypoxia can improve sports training efficiency

(Manukhina et al., 2006). Existing evidence reveals that nitric oxide (NO) is a key component of the hypoxia adaptation mechanism (Moncada, 1991; Manukhina et al., 2006). NO is synthesized from L-Arginine in the body and affects blood pressure, blood flow, and other vital body functions (Jobgen et al., 2006; LaManna et al., 2004). NO not only acts as an antioxidant (Burtscher et al., 2004) but also regulates mitochondrial metabolism and energy production (Wink et al., 2001; Lukyanova, 2005; Jobgen et al., 2006). Moreover, NO affects the activation and transcription of HIF-1α (Brüne & Zhou, 2007). Mechanisms mediated by reactive oxygen species (ROS) and reactive nitrogen species (RNS) in hypoxia and reoxygenation can cause cell damage (Li & Jackson, 2002). However, IHHT improves the efficiency of mitochondrial metabolism, avoiding excessive ROS generation (Sazontova & Arkhipenko, 2011). Synthesis of NO induced by adaptation to intermittent hypoxia activates other protective factors such as heat shock proteins (Kabakov et al., 2003), antioxidants (Dhakshinamoorthy & Porter, 2004), and prostaglandins (Mollace et al., 2005; Salvemini et al., 1993; Uno et al., 1997) to induce a holistic and long-lasting defense mechanism (Manukhina et al., 2006). In addition, the human body activates the sympathetic nervous system and increases sympathetic tone under acute hypoxia, avoiding excessive vasodilation and hypotension (Calbet, 2003). However, most subjects of these researches were patients, it is still unknow how IHHT with high intensity training will affect athletes.

In summary, acute short-term high-intensity training activates numerous fast-twitch muscles and causes reversible adaptation of slow-twitch muscles, facilitating rapid improvement of anaerobic metabolic efficiency and anaerobic endurance. Additionally, hypoxia-induced HIF-1α and NO can improve mitochondrial metabolism. How IHHT would change the physiological mechanism to adpat to higher intensity in a short time should be investigated, so athletes could applied it on training well and enhance training efficiency. Thus, we assumed that 2 days of IHHT would positively affect muscle strength output as well as improve anaerobic metabolism.

METHOD

Population

A total of 10 adults (Table 1) volunteered to cooperate with Sport Performance Diagnostic Institute in this study. Inclusion criteria consisted of the following: (1) 20-35 years of age, (2) participating in physical activity at least 3-5 days a week for 30 min a day. A questionnaire was used to know subjects' health situation, and it would be excluded when one condition was met. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Fu Jen Catholic University in Taiwan.

Table 1: Anthropometric Characteristics of the Subjects

Item	Mean ± Standard deviation
Age (years)	24.20±3.61
Height (cm)	171.10±7.49
Weight (kg)	64.20±8.61

Procedures

The experiment included a 30 m sprint test followed by 2 consecutive days of IHHT. The 30 m sprint test involved running a distance of 30 m (100% effort) for two rounds. The mean time in seconds was converted to speed to set the intensity of the training over the following two days. The 2-day IHHT was conducted with a high-speed treadmill (pulsar 3p, h/p/cosmos, Nussdorf-Traunstein, Germany) paired with an oxygen concentrator (Regalia, AirSep, Buffalo, New York, USA) both inside and outside a hypoxic chamber. The interval training was 4 × 3 × 40 s (Figure 1)**,** with the first and third sets performed at 80% of maximal effort for 30 m in hypoxia (O_2 13%) and the second and fourth sets performed at 90% of maximal effort for 30 m in normoxia (O_2 21%). Participants walked (1.4 m/s) for 60 s between repetitions, and for 3 min between sets wearing an oxygen mask (O_2 80%).

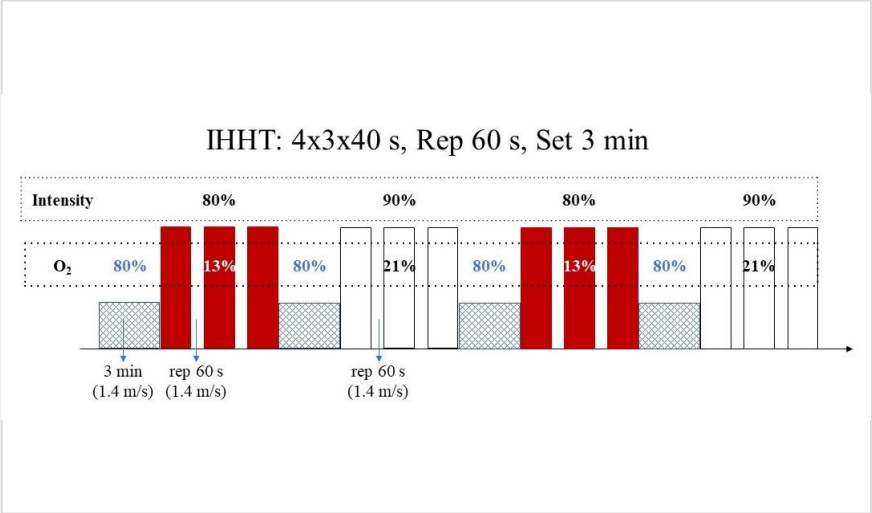

Figure 1: Experimental procedure of IHHT

Heart rate (HR), lactate (LA), ammonia (NH_3), oxygen saturation (SpO_2) were measured by an HR monitor (S725X, Polar, Kempele, Finland), glucose and lactate analyser (Diagnostics Biosen C-Line, EKF Diagnostics, Barleben, Germany), blood ammonia meter (PocketChem BA PA-4140, Arkray, Kyoto, Japan), and fingertip pulse oximeter (OxiHeart, Nissei, Gunma, Japan).

Statistical analysis

All data were presented as mean and standard deviation and were analysed and plotted using SPSS Statistics Version 22.0 (IBM, Armonk, NY, USA) and SigmaPlot 12.5 (Systat Software Inc., San Jose, California, CA, USA). Dependent sample t-test was used to analyse differences in the biological parameters between two days of training, and the significance level α was set at .05.

RESULTS

Mean HRs for Set 1 measured on the first day (Tr-1) and second day of training (Tr-2) were 178 ± 11.92 min−1 and 174 ± 9.98 min−1, respectively; a difference of 4 min−1 ($p < 0.05$). Mean HRs for Set 2 measured on Tr-1 and Tr-2 were 179 ± 10.66 min−1 and 175 ± 12.16

min−1, respectively; a difference of 4 min−1 ($p < 0.05$). Results for SpO2 were nonsignificant (Table 2).

As well as, change in blood CBC indicators shows in Table 2. The result showed significant difference between pre-season, mid- season and end- season at HCT (p=0.010), MCV (p=0.034), MCHC (p=0.001), PLT (p=0.015), PLR (p=0.011), NLR (p=0.019), and SII (p=0.25), but not ither indices ($p \geq 0.05$). Post hoc comparisons showed significant increase in HCT (p=0.008) at mid- season compared to pre-season. Also, there were significant deccrease in MCHC at mid-season (p=0.001) and end- season (p=0.001) compared to pre- season. MCV (p=0.041) and PLT (p=0.016) significantly increased at end- season compared to pre season (p=0.016). PLR and SII significantly indresed at mid-season (resoectively, p=0.013, p=0.012) and end-season (resoectively, p=0.026, p=0.042) compared to pre-season. NLR significantly increased at mid-season compared to pre-season (p=0.022) and significantly decreased at end-season compared to mid-season (p=0.019).

Table 2: HR and SpO_2 of the 2-day IHHT

	HR (min^{-1})			**SpO_2 (%)**		
	Tr-1	**Tr-2**	**Diff**	**Tr-1**	**Tr-2**	**Diff**
R	75.0±13.0	78.5±10.6	3.5±7.6	97.1±1.1	97.1±0.7	0.0±0.9
Set1	177.8±11.9	173.6±10.0	4.2±5.1*	69.1±7.5	69.4±7.1	0.3±3.6
Set2	179.3±10.7	175.3±12.2	4.0±5.5*	93.5±5.4	95.7±2.2	2.2±5.5
Set3	177.5±9.8	175.9±10.6	1.6±7.2	72.0±6.5	69.7±7.1	2.3±4.6
Set4	180.1±11.0	177.6±11.5	2.5±3.8	93.8±1.9	93.9±6.1	0.1±5.1
E5	113.3±11.5	108.3±12.3	5.0±6.9*	-	-	-

Data are presented as mean values and standard deviations (±SDs).
R, baseline; E5, the 5th minute after the end of training
* $p < 0.05$

The Tr-1–Tr-2 difference of mean LA levels for Set 3 and Set 4 were 0.96 ± 0.75 mmol/l ($p < 0.01$) and 1.05 ± 1.12 mmol/l ($p < 0.05$), respectively. At minutes 3, 7, and 10 of the recovery period (i.e., E3, E7, E10), the difference were 0.98 ± 0.83 mmol/l ($p < 0.01$), 1.21 ± 1.11 mmol/l ($p < 0.01$), and 1.11 ± 1.50 mmol/l ($p < 0.05$), respectively. Mean

NH_3 concentrations at Set 4 were 117.70 ± 29.8 μmol/l for Tr-1 and 94.50 ± 14.45 μmol/l for Tr-2; a difference of 23.2 μmol/l ($p > 0.05$), as presented in Figure2.

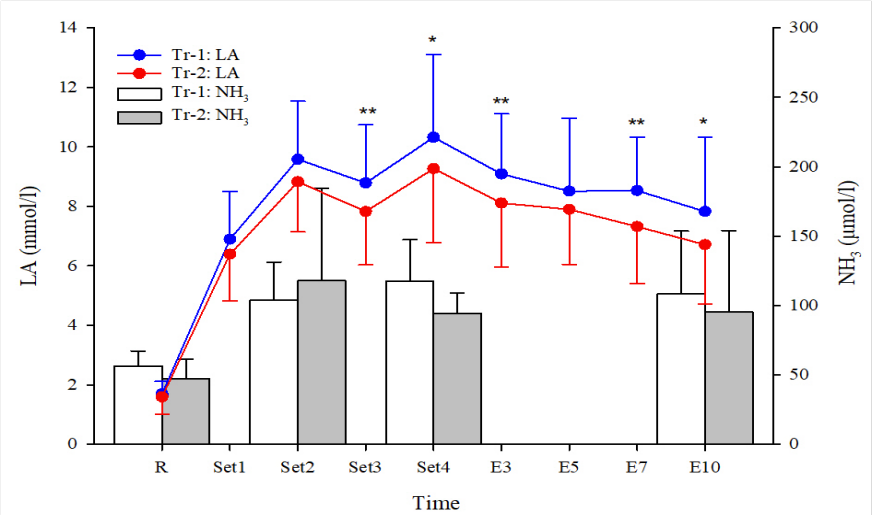

Figure 2: LA and NH_3 of the 2-day IHHT

R, baseline; E3, the 3rd minute after the end of training; E5, the 5th minute after the end of training; E7, the 7th minute after the end of training; E10, the 10th minute after the end of training

* $p < 0.05$, ** $p < 0.01$

DISCUSSION

The 2-day IHHT improved the heart's regulatory capacity during hypoxia, and the recovery capacity after training was superior to that before training. In terms of SpO_2, no overall improvements were observed. Burtscher et al. (2004) reported that a reduction in heart rate—determined by the arterial oxygen content—may be mediated by a decline in relative sympathetic tone. Intermittent hypoxia can reduce declined vagus nerve function as well as β-adrenaline receptor sensitivity (Bernardi et al., 2001; Meerson et al., 1991), which might be part of the reasons for the overall HR improvement and partial SpO_2 improvement. Studies have confirmed that the onset of hypoxia can induce tachycardia and hypertension, which can last for 10 min. Subsequently, HR and blood pressure drop sharply for up to 24 h before returning to a near-normoxic state (Kawaguchi et al., 2005; Cowburn et al., 2017). A similar phenomenon was observed for Tr-2. Raven (1998) reported that reduced

HR and systolic blood pressure during intermittent hypoxia for the same exercise load implied reduced myocardial oxygen consumption. When exercising in normoxic or hypoxic environments, blood flow and vascular endothelial cell pressure increase, resulting in NO release to regulate vascular tone and blood distribution to the desired area. NO also regulates mitochondrial metabolism and energy production (Wink et al., 2001; Lukyanova, 2005; Jobgen et al., 2006), which is critical for hypoxia adaptation (Moncada, 1991; Manukhina et al., 2006). NO also affects HIF-1α and activates gene transcription of angiogenic factors such as vascular endothelial growth factor (Brüne & Zhou, 2007) to amplify the expression of the coded proteins for angiogenesis-related genes. Blood vessels are formed by reshaping arteries through generation of endothelial cells, formation of new blood vessels from pre-existing vessels, or increased pressure at the inner walls of the blood vessels. Finally, tissue perfusion and reoxygenation were increased to overcome damage caused by hypoxia (Li & Jackson, 2002) and for adaptation (Rey & Semenza, 2010). Research on aerobic capacity related to recovery capacity has reported that hypoxic training can help improve aerobic capacity (Czuba et al, 2013; Kim et al., 2017). HIIT in a hypoxic environment was also observed to improve aerobic capacity, increase maximal oxygen uptake, induce more proangiogenesis factors, and stimulate NO synthesis to achieve endothelial-dependent vasodilation (Żebrowska et al., 2019).

The 2-day IHHT also improved participant anaerobic energy metabolism. The concurrent decrease of LA levels and NH_3 concentrations implied that dependency on carbohydrates and muscle protein as energy sources was reduced. That is, anaerobic stress imposed on the body under the same load intensity was reduced. The limited oxygen supply and decreased oxygen levels in the atmosphere during hypoxia can reduce oxygen tension during exercise. In these situations, mitochondrial biogenesis in the recruited muscles also increases (Terrados et al., 1990; Richardson et al., 1995; Melissa et al., 1997; Norrbom et al., 2004). In addition, during hypoxia HIF-1α naturally accumulates and combines with HIF-1β in the nucleus, thereby activating hypoxia-responsive genes to drive metabolic adaptation: Bcl-2/adenovirus E1B19 kDa interacting protein 3 (BNIP3) increases and causes mitochondrial autophagy. Subsequently, the efficiency of electron

transfer is improved to reduce ROS generation. The increase in glycolytic enzymes and lactate dehydrogenase facilitates anaerobic ATP production and LA generation. Finally, pyruvate dehydrogenase kinase is increased to inactivate pyruvate dehydrogenase, which limits the conversion of pyruvate to acetyl-CoA (Murray, 2009). These changes in mitochondria and the regulation of metabolism under hypoxic stimulation are all potential factors contributing to the rapid alleviation of anaerobic metabolic stress. Relevant studies have revealed that hypoxic training lasting at least 10 days can significantly improve physical work capacity (Billings et al., 1971), and that the accumulated lactate concentration at the same strength output is reduced (Maher et al., 1974). Studies have also explored differences between exercising in hypoxia and in normoxia; hypoxic training was found to significantly increase the activity of oxidase, myoglobin (Terrados et al., 1990), and citrate synthase (Bigard et al., 1991; Kaijser et al., 1990; Melissa et al., 1997). Czuba et al. (2013) also investigated HIIT in a hypoxic environment, and discovered that during exercise and the recovery period the experimental group was lower in LA than the control group. Similar research has also suggested that HIIT can result in more adaptive muscle tissue changes compared with normoxic training. These adaptive changes include increased mitochondrial density in skeletal muscle, ratio of microvessels to muscle fibers, and muscle fiber cross-sectional area (Desplanches et al., 1993; Vogt et al, 2001). IHHT as proposed in this study improved training efficiency by combining hypoxic training with intermittent training in hyperoxia. The NO produced during the load process facilitated energy regulation and metabolism of mitochondria (Wink et al., 2001; Lukyanova, 2005; Jobgen et al., 2006), induced the activation and transcription of HIF-1α (Brüne & Zhou, 2007), and reduced ROS generation (Sazontova & Arkhipenko, 2011), thereby shortening training times and resulting in improvement on Tr-2.

CONCLUSIONS

The 2-day IHHT had positive effects on the second day of the training (Tr-2) including lower HR and LA levels. NH3 was reduced, but the changes did not meet the threshold for statistical significance. Accordingly, short-term acute high-intensity training rapidly improved cardiac regulatory capacity when combined with physical hypoxia. Body

demand for carbohydrates and protein was also reduced under the same load intensity, reducing anaerobic metabolism stress.

Declaration of Interest

The authors declare that there is no conflict of interest.

Acknowledgment

The authors are grateful to the subjects who participated in the study.

REFERENCES

Bernardi, L., Passino, C., Serebrovskaya, Z., Serebrovskaya, T., & Appenzeller, O. (2001). Respiratory and cardiovascular adaptations to progressive hypoxia. European Heart Journal, 22(10), 879-886.

Bigard, A. X., Brunet, A., Guezennec, C. Y., & Monod, H. (1991). Skeletal muscle changes after endurance training at high altitude. Journal of Applied Physiology, 71(6), 2114-2121.

Billings, C. E., Bason, R. O. B. E. R. T., Mathews, D. K., & Fox, E. L. (1971). Cost of submaximal and maximal work during chronic exposure at 3,800 m. Journal of applied physiology, 30(3), 406-408.

Borg, G. (1962). A simple rating scale for use in physical work test. Håkan Ohlssons boktryckeri.

Brocherie, F., Millet, G. P., D'Hulst, G., Van Thienen, R., Deldicque, L., & Girard, O. (2018). Repeated maximal-intensity hypoxic exercise superimposed to hypoxic residence boosts skeletal muscle transcriptional responses in elite team-sport athletes. Acta Physiologica, 222(1), e12851.

Brooks, G. A., Brooks, T. G., & Brooks, S. (2008). Laktat als metabolisches Signal der Genexpression. Dtsch Z Sportmed, 59(12), 280-286.

Brüne, B., & Zhou, J. (2007). Hypoxia-inducible factor-1α under the control of nitric oxide. Methods in enzymology, 435, 463-478.

Burtscher, M., Pachinger, O., Ehrenbourg, I., Mitterbauer, G., Faulhaber, M., Pühringer, R., & Tkatchouk, E. (2004). Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. International journal of cardiology, 96(2), 247-254.

Calbet, J. A. (2003). Chronic hypoxia increases blood pressure and noradrenaline spillover in healthy humans. The Journal of physiology, 551(1), 379-386.

Cowburn, A. S., Macias, D., Summers, C., Chilvers, E. R., & Johnson, R. S. (2017). Cardiovascular adaptation to hypoxia and the role of peripheral resistance. Elife, 6, e28755.

Czuba, M., Zając, A., Maszczyk, A., Roczniok, R., Poprzęcki, S., Garbaciak, W., & Zając, T. (2013). The effects of high intensity interval training in normobaric hypoxia on aerobic capacity in basketball players. Journal of human kinetics, 39(1), 103-114.

Desplanches, D., Hoppeler, H., Linossier, M. T., Denis, C., Claassen, H., Dormois, D., ... & Geyssant, A. (1993). Effects of training in normoxia and normobaric hypoxia on human muscle ultrastructure. Pflügers Archiv, 425(3), 263-267.

Dhakshinamoorthy, S., & Porter, A. G. (2004). Nitric oxide-induced transcriptional up-regulation of protective genes by Nrf2 via the antioxidant response element counteracts apoptosis of neuroblastoma cells. Journal of Biological Chemistry, 279(19), 20096-20107.

Egan, B., Carson, B. P., Garcia-Roves, P. M., Chibalin, A. V., Sarsfield, F. M., Barron, N., ... & O'Gorman, D. J. (2010). Exercise intensity-dependent regulation of PGC-1α mRNA abundance is associated with differential activation of upstream signalling kinases in human skeletal muscle. J Physiol, 588(Pt 10), 1779-1790.

Eltzschig, H. K., Bratton, D. L., & Colgan, S. P. (2014). Targeting hypoxia signalling for the treatment of ischaemic and inflammatory diseases. Nature Reviews Drug Discovery, 13(11), 852-869.

Faiss, R., Léger, B., Vesin, J. M., Fournier, P. E., Eggel, Y., Dériaz, O., & Millet, G. P. (2013). Significant molecular and systemic adaptations after repeated sprint training in hypoxia. PloS one, 8(2), e56522.

Heinicke, K., Hofer, T., Wenger, R. H., & Gassmann, M. (2002). Die zelluläre Antwort auf Sauerstoffmangel. Deutsche Zeitschrift für Sportmedizin, 53(10), 270-276.

Hoppeler, H., & Vogt, M. (2001). Muscle tissue adaptations to hypoxia. Journal of experimental biology, 204(18), 3133-3139.

Jang, J. T., Wang, Y. C., Chen, C. H., & Chan, Y. S. (2012). Die Anpassungen eines fünftägigen Hypoxie-Trainings auf Metabolismus und Kreislauf beim 400m Läufer. Deutsche Zeitschrift für Sportmedizin. 63. 7-8. 245.

Jelkmann, W. (1992). Erythropoietin: structure, control of production, and function. Physiological reviews, 72(2), 449-489.

Jobgen, W. S., Fried, S. K., Fu, W. J., Meininger, C. J., & Wu, G. (2006). Regulatory role for the arginine–nitric oxide pathway in metabolism of energy substrates. The Journal of nutritional biochemistry, 17(9), 571-588.

Kabakov, A. E., Budagova, K. R., Bryantsev, A. L., & Latchman, D. S. (2003). Heat shock protein 70 or heat shock protein 27 overexpressed in human endothelial cells during posthypoxic reoxygenation can protect from delayed apoptosis. Cell stress & chaperones, 8(4), 335.

Kaijser, L. E. N. N. A. R. T., Sundberg, C. J., Eiken, O., Nygren, A. N. D. E. R. S., Esbjornsson, M., Sylven, C., & Jansson, E. (1990). Muscle oxidative capacity and work performance after training under local leg ischemia. Journal of Applied Physiology, 69(2), 785-787.

Karlsson, J., Astrand, P. O., & Ekblom, B. (1967). Training of the oxygen transport system in man. Journal of Applied Physiology, 22(6), 1061-1065.

Kawaguchi, T., Tsubone, H., Hori, M., Ozaki, H., & Kuwahara, M. (2005). Cardiovascular and autonomic nervous functions during acclimatization to hypoxia in conscious rats. Autonomic Neuroscience, 117(2), 97-104.

Kim, S. H., An, H. J., Choi, J. H., & Kim, Y. Y. (2017). Effects of 2-week intermittent training in hypobaric hypoxia on the aerobic energy metabolism and performance of cycling athletes with disabilities. Journal of physical therapy science, 29(6), 1116-1120.

LaManna, J. C., Chavez, J. C., & Pichiule, P. (2004). Structural and functional adaptation to hypoxia in the rat brain. Journal of Experimental Biology, 207(18), 3163-3169.

Laursen, P. B., & Jenkins, D. G. (2002). The scientific basis for high-intensity interval training. Sports medicine, 32(1), 53-73.

Li, C., & Jackson, R. M. (2002). Reactive species mechanisms of cellular hypoxia-reoxygenation injury. American Journal of Physiology-Cell Physiology, 282(2), C227-C241.

Lukyanova, L. D. (2005). Novel approach to the understanding of molecular mechanisms of adaptation to hypoxia. Adaptation Biology and Medicine, 4, 1-19.

Maher, J. T., Jones, L. G., & Hartley, L. H. (1974). Effects of high-altitude exposure on submaximal endurance capacity of men. Journal of Applied Physiology, 37(6), 895-898.

Manukhina, E. B., Downey, H. F., & Mallet, R. T. (2006). Role of nitric oxide in cardiovascular adaptation to intermittent hypoxia. Experimental Biology and Medicine, 231(4), 343-365.

McDonough, P., Behnke, B. J., Padilla, D. J., Musch, T. I., & Poole, D. C. (2005). Control of microvascular oxygen pressures in rat muscles comprised of different fibre types. The Journal of physiology, 563(3), 903-913.

Meerson, F. Z., Iun, K., & Baldenkov, G. N. (1991). Increase of alpha 1-adrenoreactivity of the rat heart in adaptation to periodic hypoxia. Biulleten'eksperimental'noi biologii i meditsiny, 111(6), 570-572.

Melissa, L. O. R. I., MacDOUGALL, J. D., Tarnopolsky, M. A., Cipriano, N. I. C. K., & Green, H. J. (1997). Skeletal muscle adaptations to training under normobaric hypoxic versus normoxic conditions. Medicine and Science in Sports and Exercise, 29(2), 238-243.

Michiels, C. (2004). Physiological and pathological responses to hypoxia. The American journal of pathology, 164(6), 1875-1882.

Millet, G. P., Girard, O., Beard, A., & Brocherie, F. (2019). Repeated sprint training in hypoxia–an innovative method. Deutsche Zeitschrift für Sportmedizin, 2019(5), 115-122.

Mollace, V., Muscoli, C., Masini, E., Cuzzocrea, S., & Salvemini, D. (2005). Modulation of prostaglandin biosynthesis by nitric oxide and nitric oxide donors. Pharmacological reviews, 57(2), 217-252.

Moncada, S. R. M. J. (1991). Nitric oxide: physiology, pathophysiology and pharmacology. Pharmacol rev, 43, 109-142.

Murray, A. J. (2009). Metabolic adaptation of skeletal muscle to high altitude hypoxia: how new technologies could resolve the controversies. Genome medicine, 1(12), 1-9.

Norrbom, J., Sundberg, C. J., Ameln, H., Kraus, W. E., Jansson, E., & Gustafsson, T. (2004). PGC-1α mRNA expression is influenced by metabolic perturbation in exercising human skeletal muscle. Journal of applied physiology, 96(1), 189-194.

Raven, P. B. (1998). Cardiovascular responses to exercise and training. Oxford Textbook of Sport Medicine.

Rey, S., & Semenza, G. L. (2010). Hypoxia-inducible factor-1-dependent mechanisms of vascularization and vascular remodelling. Cardiovascular research, 86(2), 236-242.

Richardson, R. S., Noyszewski, E. A., Kendrick, K. F., Leigh, J. S., & Wagner, P. D. (1995). Myoglobin O2 desaturation during exercise. Evidence of limited O2 transport. The Journal of clinical investigation, 96(4), 1916-1926.

Salvemini, D., Misko, T. P., Masferrer, J. L., Seibert, K., Currie, M. G., & Needleman, P. (1993). Nitric oxide activates cyclooxygenase enzymes. Proceedings of the National Academy of Sciences, 90(15), 7240-7244.

Sazontova, T. G., & Arkhipenko, Y. V. (2011). Intermittent hypoxia in resistance of cardiac membrane structures: role of reactive oxygen species and redox signaling. In Intermittent Hypoxia: From Molecular Mechanisms to Clinical Applications (pp. 113-150).

Terrados, N., Jansson, E., Sylven, C., & Kaijser, L. (1990). Is hypoxia a stimulus for synthesis of oxidative enzymes and myoglobin?. Journal of Applied Physiology, 68(6), 2369-2372.

Thomas, C., Bishop, D., Moore-Morris, T., & Mercier, J. (2007). Effects of high-intensity training on MCT1, MCT4, and NBC expressions in rat skeletal muscles: influence of chronic metabolic alkalosis. American Journal of Physiology-Endocrinology and Metabolism, 293(4), E916-E922.

Uno, H., Arakawa, T., Fukuda, T., Yu, H., Fujiwara, Y., Higuchi, K., ... & Kobayashi, K. (1997). Nitric oxide stimulates prostaglandin synthesis in cultured rabbit gastric cells. Prostaglandins, 53(3), 153-162.

Vogt, M., Puntschart, A., Geiser, J., Zuleger, C., Billeter, R., & Hoppeler, H. (2001). Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. Journal of applied physiology, 91(1), 173-182.

Wagner, P. D. (2010). Limiting factors of exercise performance. Deutsche Zeitschrift für Sportmedizin, 61(5).

Wahl, P., Bloch, W., Mester, J., & für Leistungssport, D. D. F. (2009). Moderne Betrachtungsweisen des Laktats: Laktat ein uberschatztes und zugleich unterschatztes Molekul. Schweizerische Zeitschrift fur Sportmedizin und Sporttraumatologie, 57(3), 100.

Wink, D. A., Miranda, K. M., Espey, M. G., Pluta, R. M., Hewett, S. J., Colton, C., ... & Grisham, M. B. (2001). Mechanisms of the antioxidant effects of nitric oxide. Antioxidants and redox signaling, 3(2), 203-213.

Żebrowska, A., Jastrzębski, D., Sadowska-Krępa, E., Sikora, M., & Di Giulio, C. (2019). Comparison of the effectiveness of high-intensity interval training in hypoxia and normoxia in healthy male volunteers: a pilot study. BioMed research international, 2019.

Zoll, J., Ponsot, E., Dufour, S., Doutreleau, S., Ventura-Clapier, R., Vogt, M., ... & Fluck, M. (2006). Exercise training in normobaric hypoxia in endurance runners. III. Muscular adjustments of selected gene transcripts. Journal of applied physiology, 100(4), 1258-1266.