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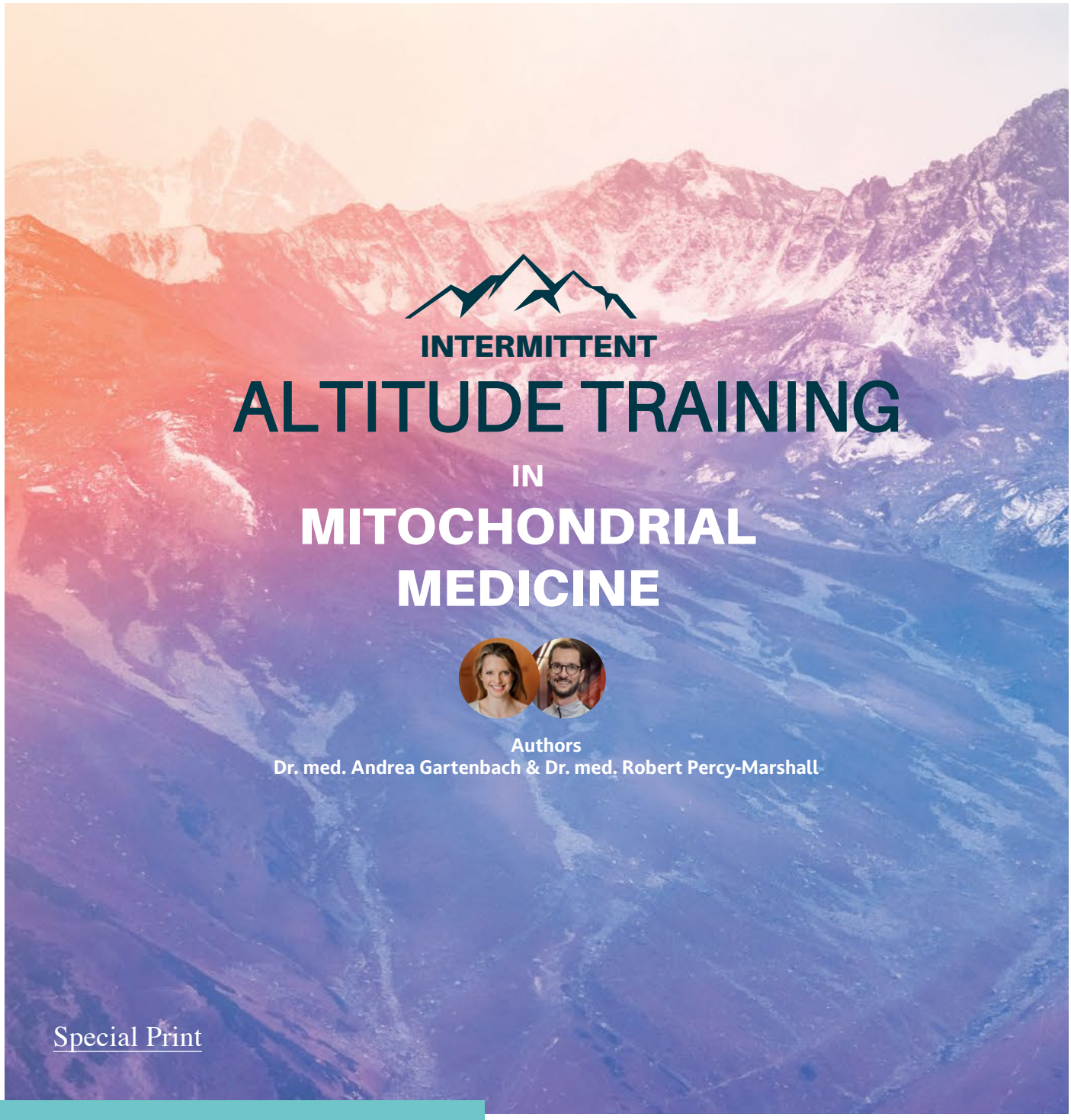

INTERMITTENT ALTITUDE TRAINING IN MITOCHONDRIAL MEDICINE

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1. INTRODUCTION

Intermittent hypoxic training (IHT) has become an integral part of many medical practices. It is valued for its health benefits as adjuvant therapy for chronic diseases and as an essential component of preventive medicine. The objective is to non-specifically increase the body's resistance through targeted mitophagy of damaged mitochondria and optimisation of cellular respiration.

Oxidative damage to mitochondrial DNA (mtDNA), which leads to mitochondrial dysfunction, is one of the primary factors in human ageing and the development of chronic diseases [1]. Continuous regeneration of mitochondria (mitophagy and mitogenesis) can reduce oxidative stress, increase the efficiency of oxidative metabolism, slow down the ageing process and prevent and/or delay the development of age-related diseases [2]. The development of mitochondrial dysfunction is primarily attributable to hypercaloric, processed food, a chronic inflammatory condition, chronic metabolic acidosis, as well as regulatory disorders of the autonomic vegetative nervous system [3, 4]. This leads to a dysregulation of the entire system with insufficient energy production despite sufficient oxygen being available (Warburg syndrome) [5].

Physiological adaptation phenomena of the human metabolism at altitude are primarily induced by the reduced oxygen content of the air we breathe (hypoxia) and by the hypobaric ambient pressure.

Only longer stays at corresponding altitudes lead to adaptation of the renal, cardiac, pulmonary and haematological organ systems. Certainly the best known physiological adaptation to altitude exposure is the increased release of erythropoietin, which leads to an increase in oxygen-transporting red blood cells (erythrocytes) and thus to improved aerobic performance [6].

While the status of 'intermittent hypoxia' is considered beneficial to health in climatotherapy, patients who suffer from obstructive sleep apnoea, and thus from unwanted intermittent hypoxia, are usually chronically ill and have multiple organic problem areas [7]. Although the same cellular sensors and signalling pathways are activated, the intensity and duration of hypoxia appear to be highly significant. It can also vary intraindividually and over the course of a person's life [8, 9].

A distinction is made between intermittent hypoxia in episodes, IHT with generators in minute intervals and permanent hypoxia [10]. We now know that therapeutically applied intermittent hypoxia can generate a variety of positive, health-promoting physiological adaptations [11]. This response can even be enhanced if the normoxic recovery phase is replaced by a hyperoxic

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recovery phase [12–14]. Based on these findings, a new form of hypoxia exposure (intermittent hypoxia-hyperoxia training, IHHT) has been developed. The alternation of these different oxygen levels has proven to be particularly effective in stimulating mitochondrial biogenesis and mitophagy [11, 15].

2. MOLECULAR MECHANISMS

IHHT induces mitochondrial recovery at the cellular level. Time-controlled and intensity-regulated hypoxia leads to a positive change in the respiratory chain without generating a negative energy balance [16, 17]. Instead, there is an increase in free oxygen radicals in the positive sense of mitohormesis [18]. A key factor here is the hypoxia-inducible factor (HIF-1α), which is activated within a very short time under hypoxic conditions [19, 20]. HIF-1α triggers several reactions aimed at improving the utilisation of oxygen by the body. HIF-1α is expressed in almost every tissue, but particularly high concentrations have been detected in neurons, which explains the special effect of IHHT on neuronal structures [21, 22]. HIF-1α is a transcription factor that increases the expression of the vascular endothelial growth factor (VEGF) and the VEGF receptors and alters the expression of genes that control glucose transport (via induction of the GLUT-4 glucose transporter). Moreover, HIF-1α induces production of the neurotransmitters serotonin, dopamine and GABA and leads to an increase in the expression of glycolytic enzymes such as aldolase, lactate dehydrogenase, phosphofructokinase and pyruvate kinase as well as erythropoietin (EPO) genes [11].

Mitochondrial therapy increases cellular energy production by switching from burning sugar to burning fat [23]. This enables the body to generate significantly more energy to cope with a stress adaptation reaction by optimising oxidative phosphorylation [24].

As previously mentioned, the excessive oxygen radicals produced in this process are reduced and the mitochondrial respiratory chain is optimised. As a result, all nutrients required by the cell can be better supplied and metabolic products can be removed more efficiently [25].

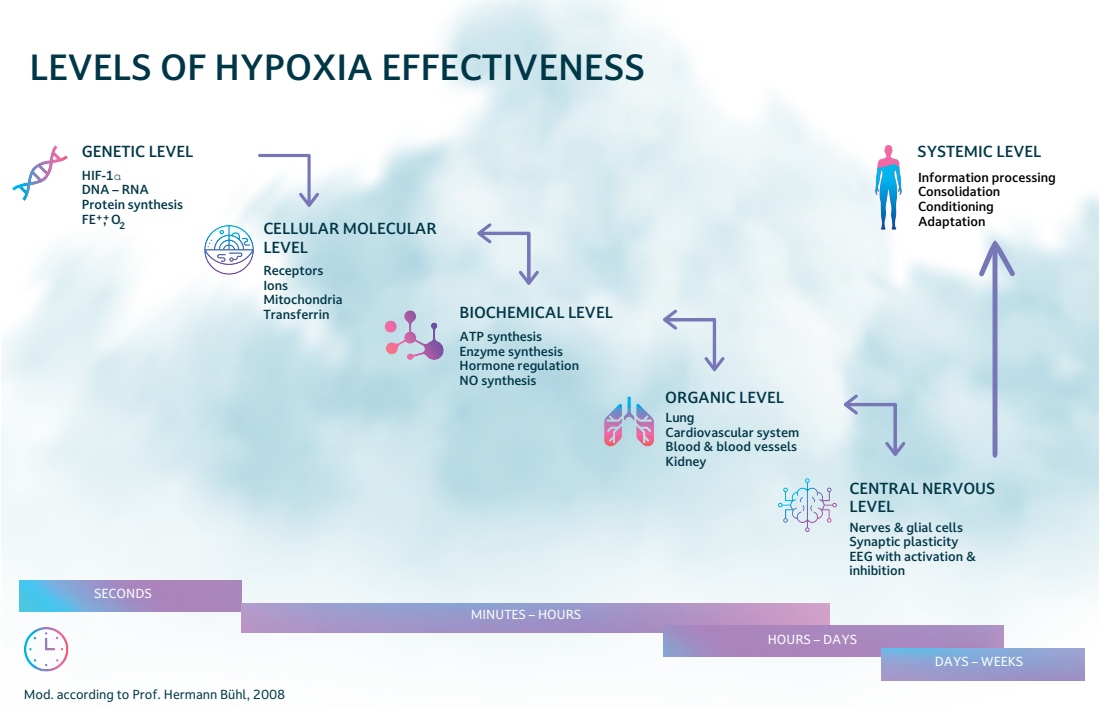
It must be emphasised that short-term intermittent hypoxic training probably only causes a small degree of erythropoietic adaptation [12], as a longer hypoxic stimulus is needed to 'stimulate the erythropoietic metabolic pathway to such an extent that it improves endurance performance after altitude exposure' [26, 27]. This assumption is supported by the fact that no significant change in total haemoglobin mass, erythrocyte volume or other erythrocyte indices was observed in previous IHT studies [12]. Similarly, organ adaptations (such as renal, pulmonary or direct cardiac effects) appear to require a more intense hypoxic stimulus to display a significant change [6, 28].

IHHT optimises nitric oxide (NO) concentrations by stimulating its synthesis while limiting its overproduction [29]. NO synthesis activates the expression of cellular protective factors, including heat shock proteins [30], antioxidants, prostaglandins and cyclooxygenase [30]. This results in reduced aggregation of platelets, leukocytes and erythrocytes as well as a reduction in the adhesion of leukocytes to the endothelial cells. NO acts on the smooth muscle walls of the blood vessels and relaxes them. Hypoxia training leads to an improvement in blood pressure by simultaneously preventing NO overproduction and NO deficiency [31].

Practising IHHT using the interval method (over several hours, several times a week) induces various biological adaptation processes.

This results in improved angiogenesis and capillarisation of the tissue, adaptation of cardiac performance, modulation of pulmonary functionality, regulation of the autonomic nervous system and influence on neurogenic structures.

> IHHT induces mitochondrial recovery at the cellular level.



HIF-1α was identified as the most important pro-angiogenic factor under hypoxic conditions [32]. Although the regulation of HIF-1α is a possible therapeutic target, it must be assessed differently depending on the clinical picture, which has an impact on potential contraindications of IHHT: in ischaemic diseases, HIF-1α upregulation would be the target [33], whereas in endometriosis and cancer, downregulation of HIF-1α is necessary [34, 35].

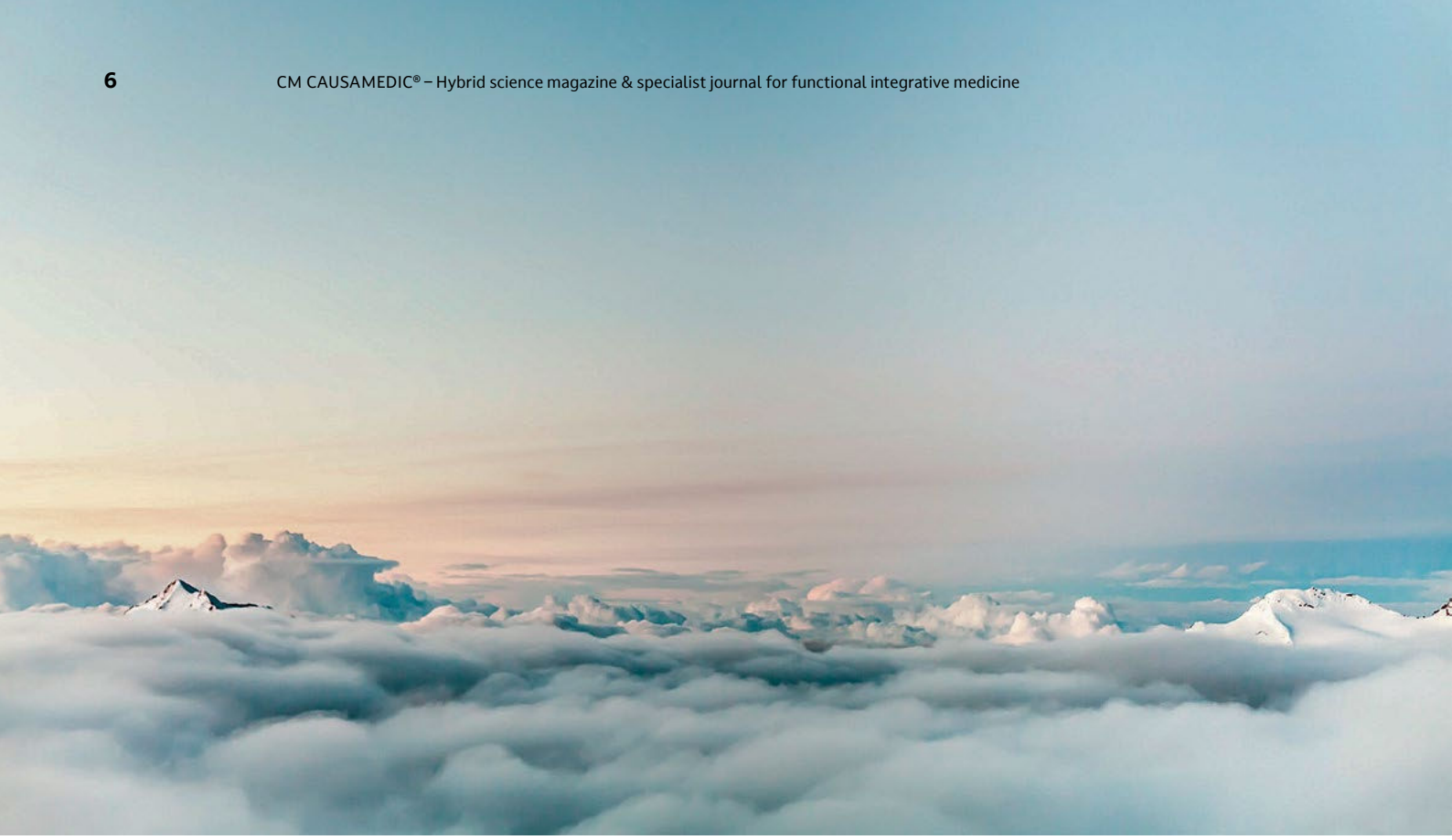
HIF-1α controls the positive regulation of BNIP3, which reduces mitochondrial mass through autophagy by activating Beclin 1 [36, 37].

This primarily drives defective mitochondria into programmed cell death, while healthy mitochondria can continue to replicate, which are selectively protected by the activation of PGC1-α and stimulation of superoxide dismutase and glutathione peroxidase [38].

3. IHHT IN THE TREATMENT OF ILLNESSES

Cardiology

The cardioprotective effects of IHHT are attributable to the preservation of mitochondrial function and the apoptotic protection of cardiomyocytes through activation of ATP-sensitive potassium channels (mitoKATP) and inhibition of the mitochondrial permeability transition pore (mPTP) [39–44]. In animal experiments, it was shown that endurance training under hypoxic conditions produces a healthy mitochondria cell phenotype, which leads to reduced apoptosis by inhibiting the mPTP [45, 46]. The experiments also showed that mitoKATP of intact ventricular cardiomyocytes begin to open within 20–25 minutes under moderate hypoxia [47]. Furthermore, the NO release resulting from regular IHHT showed an improvement in cardiac function by increasing the ATP rate of cardiomyocytes and improved coronary perfusion [48–50]



Pulmonology
Similar to patients with heart disease, exposure to high altitudes in a stimulating climate can be a considerable stressor for acute lung patients, which can lead to initial worsening of the symptoms. IHHT can avoid this initial worsening of symptoms. Regular use of IHHT in pulmonary diseases results in: (a) optimisation of the breathing control pattern [51], (b) mitochondrially optimised oxygen metabolism [52] and (c) a decrease in free radicals and an associated anti-inflammatory effect [51, 53–55]. The immunosuppressive effects previously demonstrated at high altitudes could not be reproduced in various studies using IHHT, meaning that the beneficial health factors once again significantly outweigh the negative ones [56, 57].

Neurology
Neurological adaptations to hypoxic training are controlled by the activation of Notch1 [58]. Notch1 is a transcription factor in the neuronal membrane that regulates neurogenesis and promotes differentiation of progenitor cells into astroglia [59]. Consequently, IHHT has proven to be an effective therapy for neuro-degenerative brain diseases (NEDs such as Parkinson's and Alzheimer's) with few side effects as well as other neurological conditions (epilepsy, depression) [29, 60–62]. Targeted IHHT for NED treatment led to an improvement in cognitive abilities and a positive change in specific neurodegenerative biomarkers after just 3 weeks of training (5x/week with 4 cycles each) [63]. Schega and colleagues also reported that intermittent hypoxia enhances the positive effects of exercise on cognitive function in older people [64].

4. HRV, ANS AND REGENERATION

Special focus in the field of stress and sports medicine should be placed on regeneration and supporting the ability to regenerate.

Hypoxic training has a significant influence on the autonomic nervous system (ANS). During IHHT, the measurement of heart rate variability (HRV) has therefore proven to be a useful biofeedback parameter [65–67]. Heart rate variability (HRV) is a widely used marker that reflects cardiac modulation by sympathetic and vagal components and thus the general activity of the ANS. HRV is the variation in beat-to-beat intervals (blood pressure spikes) and is commonly used to assess autonomic modulation of the heart, particularly the interaction between the sympathetic and parasympathetic nervous systems [68].

When the body is exposed to a hypoxic stimulus, the heart rate initially accelerates [69, 70]. As a result of the reduced oxygen saturation and the activation of the peripheral chemoreceptors, the sympathetic nervous system is activated, which also leads to an increase in pulse rate and peripheral vasoconstriction [71, 72]. Moreover, reflexive parasympathetic activity leads to subjective relaxation, which is especially useful for treatment of stress-induced disorders [10, 73]. This lasting improvement in vagal adaptability can be seen as a kind of induced vagus training.

Hypoxic training has a significant influence on the autonomic nervous system.

The autonomic nervous system (ANS) consists of the parasympathetic nervous system (PNS), the sympathetic nervous system (SNS) and the enteric nervous system (ENS). It regulates non-voluntary reactions of the body, above all the smooth muscles of the organs and thus their activity.

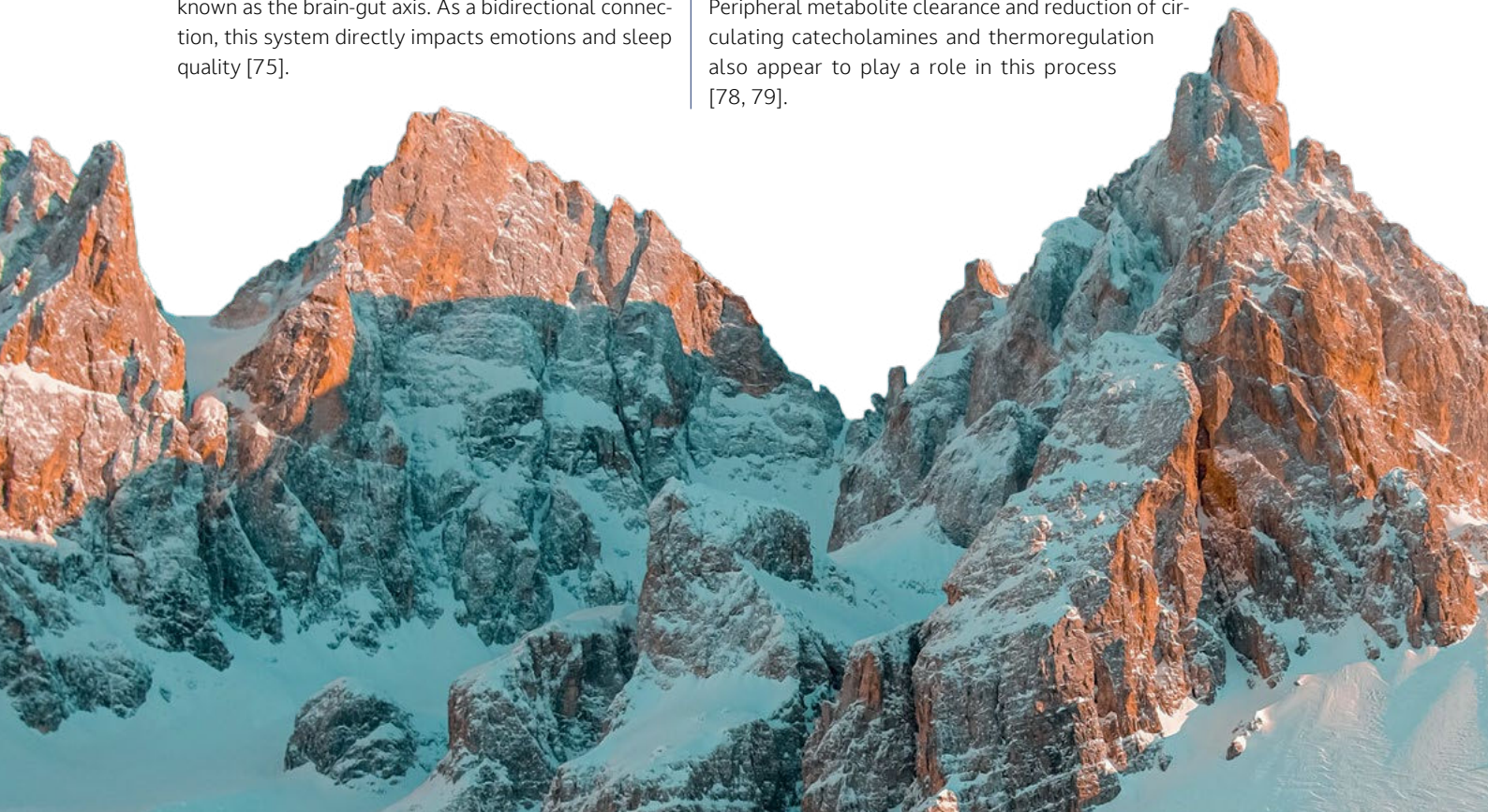
The PNS (above all the vagus nerve, the largest nerve of the parasympathetic nervous system) directly affects the body's own regulatory and regenerative abilities by physiologically supporting rest and digestion. Its cardiac and gastrointestinal fibres downregulate the heart rate and upregulate the muscle tone of the smooth intestinal muscles and enzyme secretion. Its cervical fibres constrict the pupils and enable shielding from disturbing factors [74]. The PNS thus has a direct impact on food intake, immunological reactions and sleep.

Apart from that, the vagus nerve establishes the connection between the central nervous system (CNS) and the enteric nervous system. This connection is also known as the brain-gut axis. As a bidirectional connection, this system directly impacts emotions and sleep quality [75].

In contrast to this is the sympathetic nervous system, which is also colloquially referred to as the fight or flight mode [76]. It is therefore plausible that the sympathetic nervous system is primarily active during sports activities and the parasympathetic nervous system during regeneration.

The heart rate is mainly regulated by the ANS. The mechanism of (exercise-induced) tachycardia appears to involve both parasympathetic and sympathetic reflex circuits (Bainbridge reflex). The latter mechanism is important to mention, as sympatho-adrenal stimulation predominates during exercise [77].

At the end of exercise, the aforementioned ANS circuits are reversed. The first rapid phase of heart rate recovery (drop in heart rate) is therefore often referred to as 'parasympathetic reactivation'. This is followed by a 'slow phase' of heart rate deceleration, which is probably caused by the combination of progressive reactivation of the parasympathetic nervous system and reduced activation of the sympathetic nervous system. Peripheral metabolite clearance and reduction of circulating catecholamines and thermoregulation also appear to play a role in this process [78, 79].



The higher the fitness level, the faster the parasympathetic reactivation occurs after the training stimulus and the shorter the total time required for recovery [80, 81].

The training objective is to initiate physiological adaptations that improve physical performance. The cardiovascular system plays an important role in the recovery from physical activity. The autonomic regulation of blood flow plays a particularly crucial role in thermoregulation, the supply of nutrients and the removal of waste products. Heart rate variability (HRV) can be used as a biomarker for cardiovascular recovery. The parasympathetic reactivation of the heart after a training session varies from individual to individual and appears to correlate directly with acute and medium-term recovery (supercompensation) [82].

The regenerative capacity of the ANS correlates with the individual training status, whereby optimised regulation of the ANS is associated with a higher level of performance [83].

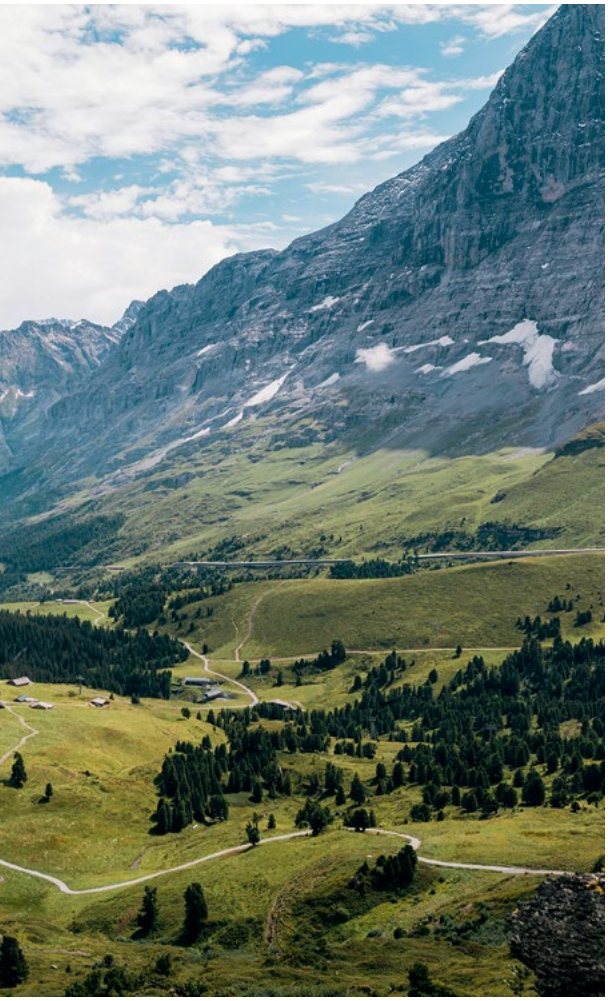
In addition to an optimised ability to regenerate, an increased tolerance to external psycho-emotional stressors also plays a key role in performance.

Adequate stress tolerance is understood as the ability of the organism to react to negative pathogenic external stimuli in a regulatory manner [84]. Stress factors cannot be avoided, but by activating the parasympathetic nervous system, the impact of stress can be quickly minimised during the competition phases [85, 86].

This led to the realisation that the vagal control of the heart should be seen as an ability that reflects the strength of self-regulation. This strength can either be exhausted or regenerated depending on the load and regeneration techniques. Laborde's group therefore introduced the term 'vagal tank' [87].

Cardiac vagal control corresponds to a barometer that reflects how efficiently self-regulation resources can be activated [88]. Consequently, this ability corresponds to the adaptability of the organism's self-regulation mechanisms [89, 90].

For a long time, it was impossible to answer the question of whether an increase in the parasympathetic nervous system is a consequence of the ability to regenerate or whether the activity of the vagus nerve possibly has a direct impact on the individual's ability to regulate. The development of HRV biofeedback training has now answered this question: HRV biofeedback treatment has been shown to have an effect on biological, psychological and performance-related areas [91]. It has been shown that interventions that have a direct positive effect on HRV measurement improve the recovery of cardiac regulatory capacity and reduce the recovery time required after training [92, 93].



Intermittent hypoxia-hyperoxia training and clinical application

During the treatment, the test subject usually lies down and wears a respiratory mask through which oxygen-reduced breathing air (18% – 9% O2) and, depending on the setting, normoxia or hyperoxia (approx. 30% O2) are inhaled alternately. The subject wears a chest strap to measure HRV and two pulse oximeters to measure peripheral oxygen saturation. The test subject is asked to relax and not to be distracted (e.g. by a mobile phone), as this has a considerable effect on the ANS.

The autonomic system and arterial oxygen saturation are the first instances to react directly to the hypoxic stimulus. In the acute phase of hypoxia, the sympathetic nervous system is primarily active. The monitoring of heart rate variability (HRV) and the change in SpO2 are therefore used as indicators for assessing the effectiveness of the treatment [11]. This ensures that the subject is not exposed to too much stress.

However, in order to set a sufficiently high physiological stress stimulus, an SpO2 value of less than 90% is pursued. An SpO2 of 73% is defined as the minimum threshold. The SpO2 limits can be redefined before each training session in order to increase or decrease the stimulus. If the level falls below the limits, the system counteracts it and a higher oxygen gas content is inhaled.

What reactions can be observed in the subject's body immediately after IHHT? A positive physiological reaction can already be seen after 15–30 minutes. Patients describe the onset of a state of general rest, often accompanied by relaxation and drowsiness as well as by a slower respiratory and heart rate. Sleep and mood improve after just one or two sessions [11]. IHHT in athletes with overtraining syndrome has been shown to reduce stress levels (i.e. lower sympathetic tone and stronger parasympathetic drive) after just a few sessions [14].

5. USE OF IHHT FOR TOP PERFORMERS

IHHT offers a plethora of short-term physiological adaptations that we can utilise for our top performers and athletes. It must be emphasised that intermittent altitude training does not lead to an adaptation of erythropoiesis [12]. Conversely, even short hypoxic training sessions have a positive effect on a significant number of genes, primarily HIF-1α and other growth factors, which leads to an indirect influence on the athlete by increasing exercise tolerance [94–96]. It also leads to regulation of vascular tone and tissue acidity (pH) as well as cellular glycolytic capacity [97]. In practical terms, this would mean a greater buffering capacity, increased lactic acid tolerance and intramuscular oxygen capacity.

IHHT can also be used regeneratively. High physical exertion leads to a local increase in lactate and a general release of oxygen radicals. Increasing the antioxidant capacity of the mitochondria can therefore lead to increased physical performance [98]. Furthermore, IHHT stimulates capillary dilation more rapidly in tissues and organs with a much lower pH and increased concentration of lactic acid (lactate) compared to non-acidified, healthy tissues [11]. Overall, it has been shown that athletes using hypoxic training regenerate better, that athletic performance can be increased more effectively as a result of training and that a lower stress level develops [57].

The importance of sleep as a regenerative factor and crucial element in performance has been discussed in detail several times in the medical field [99–101]. Especially professional athletes and top performers with international track records are regularly exposed to time differences, leading to a significantly impaired sleep pattern and reduced ability to regenerate [102–104]. IHHT has proven to be very effective, especially in stressful phases when patients complain of exhaustion, tiredness and sleep disorders. Patients describe an almost immediate onset of drowsiness, spreading of inner peace and improved sleep quality.

6. SUMMARY

Human performance is directly determined by the mitochondrial energy production of our cells. Our ability to regenerate and respond adequately to new challenges is significantly regulated by our autonomic nervous system. Healthy mitochondria and a functioning autonomic nervous system are therefore extremely important (for high performers and athletes).

Even short hypoxic training sessions have a positive effect on a significant number of genes (primarily HIF-1α and other growth factors) which leads to an indirect effect on exercise tolerance [94–96].

The influence on the cellular and nervous regeneration capacity (ANS) is enormously important for the athlete in terms of performance. In addition to positively supporting parasympathetic activity and self-regulation of the ANS, IHHT can also be actively used to support regeneration and the circadian rhythm.

IHHT is therefore a useful and effective preventative tool for maintaining performance, optimising the ability to regenerate and treating illnesses.

Literature

1. Picard, M.; Turnbull, D.M. Linking the Metabolic State and Mitochondrial DNA in Chronic Disease, Health, and Aging. Diabetes 2013, 62, 672–678, doi:10.2337/db12-1203.

2. Marshall, R.P.; Droste, J.-N.; Giessing, J.; Kreider, R.B. Role of Creatine Supplementation in Conditions Involving Mitochondrial Dysfunction: A Narrative Review. Nutrients 2022, 14, 529.

3. Diaz-Vegas, A.; Sanchez-Aguilera, P.; Krycer, J.R.; Morales, P.E.; Monsalves-Alvarez, M.; Cifuentes, M.; Rothermel, B.A.; Lavandero, S. Is Mitochondrial Dysfunction a Common Root of Noncommunicable Chronic Diseases? Endocrine Reviews 2020, 41, 491–517, doi:10.1210/endrev/bnaa005.

4. Devic, S. Warburg Effect - a Consequence or the Cause of Carcinogenesis? J Cancer 2016, 7, 817–822, doi:10.7150/jca.14274.

5. Vander Heiden, M.G.; Cantley, L.C.; Thompson, C.B. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science 2009, 324, 1029–1033, doi:10.1126/science.1160809.

6. Droste, J.-N. Umweltbedingungen. In Sportwissenschaft; Elsevier, 2022; pp. 261–269.

7. Viscor, G.; Ricart, A.; Pages, T.; Corral, L.; Javierre, C.F.; Ventura, J.L. Intermittent Hypoxia for Obstructive Sleep Apnea? High Altitude Medicine & Biology 2014, 15, 520–521.

8. Canouï-Poitrine, F.; Veerabudun, K.; Larmignat, P.; Letournel, M.; Bastuji-Garin, S.; Richalet, J.-P. Risk Prediction Score for Severe High Altitude Illness: A Cohort Study. PLoS One 2014, 9, e100642.

9. Richalet, J.-P.; Lhuissier, F.J. Aging, Tolerance to High Altitude, and Cardiorespiratory Response to Hypoxia. High altitude medicine & biology 2015, 16, 117–124.

10. Viscor, G.; Torrella, J.R.; Corral, L.; Ricart, A.; Javierre, C.; Pages, T.; Ventura, J.L. Physiological and Biological Responses to Short-Term Intermittent Hypobaric Hypoxia Exposure: From Sports and Mountain Medicine to New Biomedical Applications. Frontiers in Physiology 2018, 9.

11. Voronina, T.; Grechko, N.; Shikhlyarova, A.; Bobkova, N. Intermittent Hypoxic Training as an Effective Method of Activation Therapy. Cardiometry 2017.

12. Faiss, R.; Girard, O.; Millet, G.P. Advancing Hypoxic Training in Team Sports: From Intermittent Hypoxic Training to Repeated Sprint Training in Hypoxia. British journal of sports medicine 2013, 47, i45–i50.

13. Sanchez, A.M.J.; Borrani, F. Effects of Intermittent Hypoxic Training Performed at High Hypoxia Level on Exercise Performance in Highly Trained Runners. Journal of Sports Sciences 2018, 36, 2045–2052, doi:10.1080/02640414.2018.1434747.

14. Susta, D.; Dudnik, E.; Glazachev, O.S. A Programme Based on Repeated Hypoxia-Hyperoxia Exposure and Light Exercise Enhances Performance in Athletes with Overtraining Syndrome: A Pilot Study. Clin Physiol Funct Imaging 2017, 37, 276–281, doi:10.1111/cpf.12296.

15. Lukyanova, L.D.; Dudchenko, A.V.; Germanova, E.L.; Tsybina, T.A.; Kapaladze, R.A.; Ehrenbourg, I.V.; Tkatchouk, E.N. Mitochondrial Signaling in Formation of Body Resistance to Hypoxia. In Intermittent hypoxia: from molecular mechanisms to clinical applications; 2011; pp. 391–417.

16. Semenza, G.L. Regulation of Oxygen Homeostasis by Hypoxia-Inducible Factor 1. Physiology (Bethesda) 2009, 24, 97–106, doi:10.1152/physiol.00045.2008.

17. Fukuda, R.; Zhang, H.; Kim, J.; Shimoda, L.; Dang, C.V.; Semenza, G.L. HIF-1 Regulates Cytochrome Oxidase Subunits to Optimize Efficiency of Respiration in Hypoxic Cells. Cell 2007, 129, 111–122, doi:10.1016/j.cell.2007.01.047.

18. Ristow, M. Unraveling the Truth about Antioxidants: Mitohormesis Explains ROS-Induced Health Benefits. Nat Med 2014, 20, 709–711, doi:10.1038/nm.3624.

19. Jiang, B.H.; Semenza, G.L.; Bauer, C.; Marti, H.H. Hypoxia-Inducible Factor 1 Levels Vary Exponentially over a Physiologically Relevant Range of O2 Tension. Am J Physiol 1996, 271, C1172-1180, doi:10.1152/ajpcell.1996.271.4.C1172.

20. Wang, G.L.; Jiang, B.H.; Rue, E.A.; Semenza, G.L. Hypoxia-Inducible Factor 1 Is a Basic-Helix-Loop-Helix-PAS Heterodimer Regulated by Cellular O2 Tension. Proc Natl Acad Sci U S A 1995, 92, 5510–5514, doi:10.1073/pnas.92.12.5510.

21. Semenza, G.L. Hydroxylation of HIF-1: Oxygen Sensing at the Molecular Level. Physiology 2004, 19, 176–182.

22. Yu, A.Y.; Frid, M.G.; Shimoda, L.A.; Wiener, C.M.; Stenmark, K.; Semenza, G.L. Temporal, Spatial, and Oxygen-Regulated Expression of Hypoxia-Inducible Factor-1 in the Lung. American Journal of Physiology-Lung Cellular and Molecular Physiology 1998, 275, L818–L826.

23. Zhao, Y.-C.; Guo, W.; Gao, B.-H. Hypoxic Training Upregulates Mitochondrial Turnover and Angiogenesis of Skeletal Muscle in Mice. Life Sci 2022, 291, 119340, doi:10.1016/j.lfs.2021.119340.

24. Tsai, H.-H.; Chang, S.-C.; Chou, C.-H.; Weng, T.-P.; Hsu, C.-C.; Wang, J.-S. Exercise Training Alleviates Hypoxia-Induced Mitochondrial Dysfunction in the Lymphocytes of Sedentary Males. Sci Rep 2016, 6, 35170, doi:10.1038/srep35170.

25. Kim, J.; Tchernyshyov, I.; Semenza, G.L.; Dang, C.V. HIF-1-Mediated Expression of Pyruvate Dehydrogenase Kinase: A Metabolic Switch Required for Cellular Adaptation to Hypoxia. Cell Metab 2006, 3, 177–185, doi:10.1016/j.cmet.2006.02.002.

26. Levine, B.D.; Stray-Gundersen, J. Dose-Response of Altitude Training: How Much Altitude Is Enough? Hypoxia and Exercise 2006, 233–247.

27. Wilber, R.L.; Stray-Gundersen, J.; Levine, B.D. Effect of Hypoxic "Dose" on Physiological Responses and Sea-Level Performance. Medicine and science in sports and exercise 2007, 39, 1590–1599.

28. Rozova, K.; Mankovska, I. The Effect of Intermittent Hypoxic Training on Lung and Heart Tissues of Healthy Rats. Pneumonol Alergol Pol 2012, 80, 296–300.

29. Manukhina, E.B.; Downey, H.F.; Shi, X.; Mallet, R.T. Intermittent Hypoxia Training Protects Cerebrovascular Function in Alzheimer's Disease. Experimental Biology and Medicine 2016, 241, 1351–1363.

30. Davidge, S.T.; Baker, P.N.; McLaughlin, M.K.; Roberts, J.M. Nitric Oxide Produced by Endothelial Cells Increases Production of Eicosanoids through Activation of Prostaglandin H Synthase. Circulation research 1995, 77, 274–283.

31. Manukhina, E.B.; Downey, H.F.; Mallet, R.T. Role of Nitric Oxide in Cardiovascular Adaptation to Intermittent Hypoxia. Experimental Biology and Medicine 2006, 231, 343–365.

32. Rey, S.; Semenza, G.L. Hypoxia-Inducible Factor-1-Dependent Mechanisms of Vascularization and Vascular Remodelling. Cardiovascular research 2010, 86, 236–242.

33. Li, X.; Zhao, H.; Wu, Y.; Zhang, S.; Zhao, X.; Zhang, Y.; Wang, J.; Wang, J.; Liu, H. Up-Regulation of Hypoxia-Inducible Factor-1α Enhanced the Cardioprotective Effects of Ischemic Postconditioning in Hyperlipidemic Rats. Acta Biochim Biophys Sin 2014, 46, 112–118.

34. Zhou, S.; Yi, T.; Liu, R.; Bian, C.; Qi, X.; He, X.; Wang, K.; Li, J.; Zhao, X.; Huang, C. Proteomics Identification of Annexin A2 as a Key Mediator in the Metastasis and Proangiogenesis of Endometrial Cells in Human Adenomyosis. Molecular & cellular proteomics 2012, 11, M112-017988.

35. Bhattarai, D.; Xu, X.; Lee, K. Hypoxia-Inducible Factor-1 (HIF-1) Inhibitors from the Last Decade (2007 to 2016): A "Structure–Activity Relationship" Perspective. Medicinal research reviews 2018, 38, 1404–1442.

36. Wang, Y.; Pu, L.; Li, Z.; Hu, X.; Jiang, L. Hypoxia-Inducible Factor-1α Gene Expression and Apoptosis in Ischemia-Reperfusion Injury: A Rat Model of Early-Stage Pressure Ulcer. Nurs Res 2016, 65, 35–46, doi:10.1097/NNR.0000000000000132.

37. Zhang, H.; Bosch-Marce, M.; Shimoda, L.A.; Tan, Y.S.; Baek, J.H.; Wesley, J.B.; Gonzalez, F.J.; Semenza, G.L. Mitochondrial Autophagy Is an HIF-1-Dependent Adaptive Metabolic Response to Hypoxia. J Biol Chem 2008, 283, 10892–10903, doi:10.1074/jbc.M800102200.

38. Semenza, G.L. Hypoxia-Inducible Factors: Coupling Glucose Metabolism and Redox Regulation with Induction of the Breast Cancer Stem Cell Phenotype. EMBO J 2017, 36, 252–259, doi:10.15252/embj.201695204.

39. Ostádal, B.; Kolár, F.; Pelouch, V.; Bass, A.; Samánek, M.; Procházka, J. The Effect of Chronic Hypoxia on the Developing Cardiopulmonary System. Biomed Biochim Acta 1989, 48, S58-62.

40. Asemu, G.; Papousek, F.; Ostádal, B.; Kolár, F. Adaptation to High Altitude Hypoxia Protects the Rat Heart against Ischemia-Induced Arrhythmias. Involvement of Mitochondrial K(ATP) Channel. J Mol Cell Cardiol 1999, 31, 1821–1831, doi:10.1006/jmcc.1999.1013.

41. Chouabe, C.; Ricci, E.; Amsellem, J.; Blaineau, S.; Dalmaz, Y.; Favier, R.; Pequignot, J.-M.; Bonvallet, R. Effects of Aging on the Cardiac Remodeling Induced by Chronic High-Altitude Hypoxia in Rat. Am J Physiol Heart Circ Physiol 2004, 287, H1246-1253, doi:10.1152/ajpheart.00199.2004.

42. Ostadal, B.; Kolar, F. Cardiac Adaptation to Chronic High-Altitude Hypoxia: Beneficial and Adverse Effects. Respir Physiol Neurobiol 2007, 158, 224–236, doi:10.1016/j.resp.2007.03.005.

43. Bu, H.; Yang, C.; Wang, M.; Ma, H.; Sun, H.; Zhang, Y. K(ATP) Channels and MPTP Are Involved in the Cardioprotection Bestowed by Chronic Intermittent Hypobaric Hypoxia in the Developing Rat. J Physiol Sci 2015, 65, 367–376, doi:10.1007/s12576-015-0376-5.

44. Mallet, R.T.; Manukhina, E.B.; Ruelas, S.S.; Caffrey, J.L.; Downey, H.F. Cardioprotection by Intermittent Hypoxia Conditioning: Evidence, Mechanisms, and Therapeutic Potential. American Journal of Physiology-Heart and Circulatory Physiology 2018, 315, H216–H232, doi:10.1152/ajpheart.00060.2018.

45. Magalhães, J.; Falcão-Pires, I.; Gonçalves, I.O.; Lumini-Oliveira, J.; Marques-Aleixo, I.; Dos Passos, E.; Rocha-Rodrigues, S.; Machado, N.G.; Moreira, A.C.; Miranda-Silva, D.; et al. Synergistic Impact of Endurance Training and Intermittent Hypobaric Hypoxia on Cardiac Function and Mitochondrial Energetic and Signaling. Int J Cardiol 2013, 168, 5363–5371, doi:10.1016/j.ijcard.2013.08.001.

46. Magalhães, J.; Gonçalves, I.O.; Lumini-Oliveira, J.; Marques-Aleixo, I.; Passos, E.; Rocha-Rodrigues, S.; Machado, N.G.; Moreira, A.C.; Rizo, D.; Viscor, G.; et al. Modulation of Cardiac Mitochondrial Permeability Transition and Apoptotic Signaling by Endurance Training and Intermittent Hypobaric Hypoxia. Int J Cardiol 2014, 173, 40–45, doi:10.1016/j.ijcard.2014.02.011.

47. Babenko, A.P.; Kazantseva, S.T.; Romanova, Y.V. The Mechanisms of Activation Of the ATP-Sensitive Potassium Channels of the Sarcolemma Of Cardiomyocytes In Hypoxia. In Proceedings of the Materials of the VII All-Russian Symposium on Ecological and Physiological Problems of Adaptation. M; 1994.

48. Reynafarje, B.D.; Marticorena, E. Bioenergetics of the Heart at High Altitude: Environmental Hypoxia Imposes Profound Transformations on the Myocardial Process of ATP Synthesis. J Bioenerg Biomembr 2002, 34, 407–412, doi:10.1023/a:1022597523483.

49. del Pilar Valle, M.; García-Godos, F.; Woolcott, O.O.; Marticorena, J.M.; Rodríguez, V.; Gutiérrez, I.; Fernández-Dávila, L.; Contreras, A.; Valdivia, L.; Robles, J.; et al. Improvement of Myocardial Perfusion in Coronary Patients after Intermittent Hypobaric Hypoxia. J Nucl Cardiol 2006, 13, 69–74, doi:10.1016/j.nuclcard.2005.11.008.

50. Panisello, P.; Torrella, J.R.; Pagés, T.; Viscor, G. Capillary Supply and Fiber Morphometry in Rat Myocardium after Intermittent Exposure to Hypobaric Hypoxia. High Alt Med Biol 2007, 8, 322–330, doi:10.1089/ham.2007.1030.

51. Serebrovskaya, T.V.; Swanson, R.J.; Kolesnikova, E.E. Intermittent Hypoxia: Mechanisms of Action and Some Applications to Bronchial Asthma Treatment. J Physiol Pharmacol 2003, 54 Suppl 1, 35–41.

52. Levett, D.Z.; Radford, E.J.; Menassa, D.A.; Graber, E.F.; Morash, A.J.; Hoppeler, H.; Clarke, K.; Martin, D.S.; Ferguson-Smith, A.C.; Montgomery, H.E.; et al. Acclimatization of Skeletal Muscle Mitochondria to High-Altitude Hypoxia during an Ascent of Everest. FASEB J 2012, 26, 1431–1441, doi:10.1096/fj.11-197772.

53. Simon, H.U.; Grotzer, M.; Nikolaizik, W.H.; Blaser, K.; Schöni, M.H. High Altitude Climate Therapy Reduces Peripheral Blood T Lymphocyte Activation, Eosinophilia, and Bronchial Obstruction in Children with House-Dust Mite Allergic Asthma. Pediatr Pulmonol 1994, 17, 304–311, doi:10.1002/ppul.1950170507.

54. Ohta, A.; Diwanji, R.; Kini, R.; Subramanian, M.; Ohta, A.; Sitkovsky, M. In Vivo T Cell Activation in Lymphoid Tissues Is Inhibited in the Oxygen-Poor Microenvironment. Front Immunol 2011, 2, 27, doi:10.3389/fimmu.2011.00027.

55. Oliver, S.J.; Macdonald, J.H.; Harper Smith, A.D.; Lawley, J.S.; Gallagher, C.A.; Di Felice, U.; Walsh, N.P. High Altitude Impairs in Vivo Immunity in Humans. High Alt Med Biol 2013, 14, 144–149, doi:10.1089/ham.2012.1070.

56. Meehan, R.T. Immune Suppression at High Altitude. Ann Emerg Med 1987, 16, 974–979, doi:10.1016/s0196-0644(87)80743-6.

57. Jung, W.-S.; Kim, S.-W.; Park, H.-Y. Interval Hypoxic Training Enhances Athletic Performance and Does Not Adversely Affect Immune Function in Middle- and Long-Distance Runners. International Journal of Environmental Research and Public Health 2020, 17, 1934, doi:10.3390/ijerph17061934.

58. Gustafsson, M.V.; Zheng, X.; Pereira, T.; Gradin, K.; Jin, S.; Lundkvist, J.; Ruas, J.L.; Poellinger, L.; Lendahl, U.; Bondesson, M. Hypoxia Requires Notch Signaling to Maintain the Undifferentiated Cell State. Dev Cell 2005, 9, 617–628, doi:10.1016/j.devcel.2005.09.010.

59. Zhang, K.; Zhao, T.; Huang, X.; Wu, L.; Wu, K.; Zhu, L.; Fan, M. Notch1 Mediates Postnatal Neurogenesis in Hippocampus Enhanced by Intermittent Hypoxia. Neurobiol Dis 2014, 64, 66–78, doi:10.1016/j.nbd.2013.12.010.

60. Manukhina, E.B.; Goryacheva, A.V.; Pshennikova, M.G.; Malyshev, I.Y.; Mallet, R.T.; Downey, H.F. Protective Effects of Adaptation to Hypoxia in Experimental Alzheimer's Disease. In Intermittent Hypoxia and Human Diseases; Springer, 2012; pp. 155–171.

61. Belikova, M.V.; Kolesnikova, E.E.; Serebrovskaya, T.V. Intermittent Hypoxia and Experimental Parkinson's Disease. In Intermittent Hypoxia and Human Diseases; Springer, 2012; pp. 147–153.

62. Correia, S.C.; Moreira, P.I. Hypoxia-Inducible Factor 1: A New Hope to Counteract Neurodegeneration? J Neurochem 2010, 112, 1–12, doi:10.1111/j.1471-4159.2009.06443.x.

63. Serebrovska, Z.O.; Serebrovska, T.V.; Kholin, V.A.; Tumanovska, L.V.; Shysh, A.M.; Pashevin, D.A.; Goncharov, S.V.; Stroy, D.; Grib, O.N.; Shatylo, V.B.; et al. Intermittent Hypoxia-Hyperoxia Training Improves Cognitive Function and Decreases Circulating Biomarkers of Alzheimer's Disease in Patients with Mild Cognitive Impairment: A Pilot Study. Int J Mol Sci 2019, 20, E5405, doi:10.3390/ijms20215405.

64. Schega, L.; Peter, B.; Törpel, A.; Mutschler, H.; Isermann, B.; Hamacher, D. Effects of Intermittent Hypoxia on Cognitive Performance and Quality of Life in Elderly Adults: A Pilot Study. Gerontology 2013, 59, 316–323, doi:10.1159/000350927.

65. Hainsworth, R.; Drinkhill, M.J.; Rivera-Chira, M. The Autonomic Nervous System at High Altitude. Clin Auton Res 2007, 17, 13–19, doi:10.1007/s10286-006-0395-7.

66. Kanai, M.; Nishihara, F.; Shiga, T.; Shimada, H.; Saito, S. Alterations in Autonomic Nervous Control of Heart Rate among Tourists at 2700 and 3700m above Sea Level. Wilderness & Environmental Medicine 2001, 12, 8–12, doi:10.1580/1080-6032(2001)012[0008:AIANCO]2.0.CO;2.

67. Farinelli, C.C.; Kayser, B.; Binzoni, T.; Cerretelli, P.; Girardier, L. Autonomic Nervous Control of Heart Rate at Altitude (5050 m). Eur J Appl Physiol Occup Physiol 1994, 69, 502–507, doi:10.1007/BF00239867.

68. Taralov, Z.; Terziyski, K.; Dimov, P.; Marinov, B.; Tarvainen, M.P.; Perini, R.; Kostianev, S. Assessment of the Acute Impact of Normobaric Hypoxia as a Part of an Intermittent Hypoxic Training on Heart Rate Variability. Cor et Vasa 2015, 57, e251–e256, doi:10.1016/j.crvasa.2015.05.010.

69. Paralikar, S.J.; Paralikar, J.H. High-Altitude Medicine. Indian Journal of Occupational and Environmental Medicine 2010, 14, 6, doi:10.4103/0019-5278.64608.

70. Peacock, A.J. Oxygen at High Altitude. BMJ 1998, 317, 1063–1066, doi:10.1136/bmj.317.7165.1063.

71. BERNARDI, L.; PASSINO, C.; SPADACINI, G.; CALCIATI, A.; ROBERGS, R.; GREENE, R.; MARTIGNONI, E.; ANAND, I.; APPENZELLER, O. Cardiovascular Autonomic Modulation and Activity of Carotid Baroreceptors at Altitude. Clinical Science 1998, 95, 565–573, doi:10.1042/cs0950565.

72. Marshall, J.M. Chemoreceptors and Cardiovascular Control in Acute and Chronic Systemic Hypoxia. Braz J Med Biol Res 1998, 31, 863–888, doi:10.1590/S0100-879X1998000700002.

73. Bobyleva, O.V.; Glazachev, O.S. Changes in Autonomic Response and Resistance to Acute Graded Hypoxia during Intermittent Hypoxic Training. Hum Physiol 2007, 33, 199–206, doi:10.1134/S0362119707020107.

74. T, B.; Kn, B. The Role of Vagal Neurocircuits in the Regulation of Nausea and Vomiting. European journal of pharmacology 2014, 722, doi:10.1016/j.ejphar.2013.08.047.

75. Breit, S.; Kupferberg, A.; Rogler, G.; Hasler, G. Vagus Nerve as Modulator of the Brain-Gut Axis in Psychiatric and Inflammatory Disorders. Front Psychiatry 2018, 9, 44, doi:10.3389/fpsyt.2018.00044.

76. LeBouef, T.; Yaker, Z.; Whited, L. Physiology, Autonomic Nervous System. In StatPearls; StatPearls Publishing: Treasure Island (FL), 2022.

77. Aubert, A.E.; Seps, B.; Beckers, F. Heart Rate Variability in Athletes. Sports Med 2003, 33, 889–919, doi:10.2165/00007256-200333120-00003.

78. Michael, S.; Graham, K.S.; Davis, G.M. Cardiac Autonomic Responses during Exercise and Post-Exercise Recovery Using Heart Rate Variability and Systolic Time Intervals-A Review. Front Physiol 2017, 8, 301, doi:10.3389/fphys.2017.00301.

79. Buchheit, M.; Papelier, Y.; Laursen, P.B.; Ahmaidi, S. Noninvasive Assessment of Cardiac Parasympathetic Function: Postexercise Heart Rate Recovery or Heart Rate Variability? Am J Physiol Heart Circ Physiol 2007, 293, H8-10, doi:10.1152/ajpheart.00335.2007.

80. Cipryan, L. The Effect of Fitness Level on Cardiac Autonomic Regulation, IL-6, Total Antioxidant Capacity, and Muscle Damage Responses to a Single Bout of High-Intensity Interval Training. J Sport Health Sci 2018, 7, 363–371, doi:10.1016/j.jshs.2016.11.001.

81. Dixon, E.M.; Kamath, M.V.; McCartney, N.; Fallen, E.L. Neural Regulation of Heart Rate Variability in Endurance Athletes and Sedentary Controls. Cardiovasc Res 1992, 26, 713–719, doi:10.1093/cvr/26.7.713.

82. Stanley, J.; Peake, J.M.; Buchheit, M. Cardiac Parasympathetic Reactivation Following Exercise: Implications for Training Prescription. Sports Med 2013, 43, 1259–1277, doi:10.1007/s40279-013-0083-4.

83. Seiler, S.; Haugen, O.; Kuffel, E. Autonomic Recovery after Exercise in Trained Athletes: Intensity and Duration Effects. Med Sci Sports Exerc 2007, 39, 1366–1373, doi:10.1249/mss.0b013e318060f17d.

84. Korobeynikov, G.; Korobeynikova, L.; Potop, V.; Nikonorov, D.; Semenenko, V.; Dakal, N.; Mischuk, D. Heart Rate Variability System in Elite Athletes with Different Levels of Stress Resistance. Journal of Physical Education and Sport 2018, 18, 550–554.

85. Barbas, I.; Fatouros, I.G.; Douroudos, I.I.; Chatzinikolaou, A.; Michailidis, Y.; Draganidis, D.; Jamurtas, A.Z.; Nikolaidis, M.G.; Parotsidis, C.; Theodorou, A.A.; et al. Physiological and Performance Adaptations of Elite Greco-Roman Wrestlers during a One-Day Tournament. Eur J Appl Physiol 2011, 111, 1421–1436, doi:10.1007/s00421-010-1761-7.

86. Vladimir, P. Assessment of Physical and Technical Training Level in Basic Specialization Stage in Women's Artistic Gymnastics. Journal of physical education and sport 2013, 13, 114.

87. Laborde, S.; Mosley, E.; Mertgen, A. Vagal Tank Theory: The Three Rs of Cardiac Vagal Control Functioning - Resting, Reactivity, and Recovery. Front Neurosci 2018, 12, 458, doi:10.3389/fnins.2018.00458.

88. Hottenrott, L.; Ketelhut, S.; Hottenrott, K. Commentary: Vagal Tank Theory: The Three Rs of Cardiac Vagal Control Functioning - Resting, Reactivity, and Recovery. Front Neurosci 2019, 13, 1300, doi:10.3389/fnins.2019.01300.

89. Porges, S.W. The Polyvagal Perspective. Biol Psychol 2007, 74, 116–143, doi:10.1016/j.biopsycho.2006.06.009.

90. Thayer, J.F.; Ahs, F.; Fredrikson, M.; Sollers, J.J.; Wager, T.D. A Meta-Analysis of Heart Rate Variability and Neuroimaging Studies: Implications for Heart Rate Variability as a Marker of Stress and Health. Neurosci Biobehav Rev 2012, 36, 747–756, doi:10.1016/j.neubiorev.2011.11.009.

91. Lehrer, P.; Kaur, K.; Sharma, A.; Shah, K.; Huseby, R.; Bhavsar, J.; Sgobba, P.; Zhang, Y. Heart Rate Variability Biofeedback Improves Emotional and Physical Health and Performance: A Systematic Review and Meta Analysis. Applied Psychophysiology and Biofeedback 2020, 45, 109–129.

92. Peçanha, T.; Bartels, R.; Brito, L.C.; Paula-Ribeiro, M.; Oliveira, R.S.; Goldberger, J.J. Methods of Assessment of the Post-Exercise Cardiac Autonomic Recovery: A Methodological Review. Int J Cardiol 2017, 227, 795–802, doi:10.1016/j.ijcard.2016.10.057.

93. Perez-Gaido, M.; Lalanza, J.F.; Parrado, E.; Capdevila, L. Can HRV Biofeedback Improve Short-Term Effort Recovery? Implications for Intermittent Load Sports. Appl Psychophysiol Biofeedback 2021, 46, 215–226, doi:10.1007/s10484-020-09495-8.

94. Semenza, G.L.; Shimoda, L.A.; Prabhakar, N.R. Regulation of Gene Expression by HIF-1. Novartis Found Symp 2006, 272, 2–8; discussion 8-14, 33–36.

95. Vogt, M.; Puntschart, A.; Geiser, J.; Zuleger, C.; Billeter, R.; Hoppeler, H. Molecular Adaptations in Human Skeletal Muscle to Endurance Training under Simulated Hypoxic Conditions. J Appl Physiol (1985) 2001, 91, 173–182, doi:10.1152/jappl.2001.91.1.173.

96. Brocherie, F.; Millet, G.P.; D'Hulst, G.; Van Thienen, R.; Deldicque, L.; Girard, O. Repeated Maximal-Intensity Hypoxic Exercise Superimposed to Hypoxic Residence Boosts Skeletal Muscle Transcriptional Responses in Elite Team-Sport Athletes. Acta Physiol (Oxf) 2018, 222, doi:10.1111/apha.12851.

97. Girard, O.; Brocherie, F.; Goods, P.S.R.; Millet, G.P. An Updated Panorama of "Living Low-Training High" Altitude/Hypoxic Methods. Frontiers in Sports and Active Living 2020, 2.

98. Finaud, J.; Lac, G.; Filaire, E. Oxidative Stress : Relationship with Exercise and Training. Sports Med 2006, 36, 327–358, doi:10.2165/00007256-200636040-00004.

99. Venter, R.E. Role of Sleep in Performance and Recovery of Athletes: A Review Article. South African Journal for Research in Sport, Physical Education and Recreation 2012, 34, 167–184.

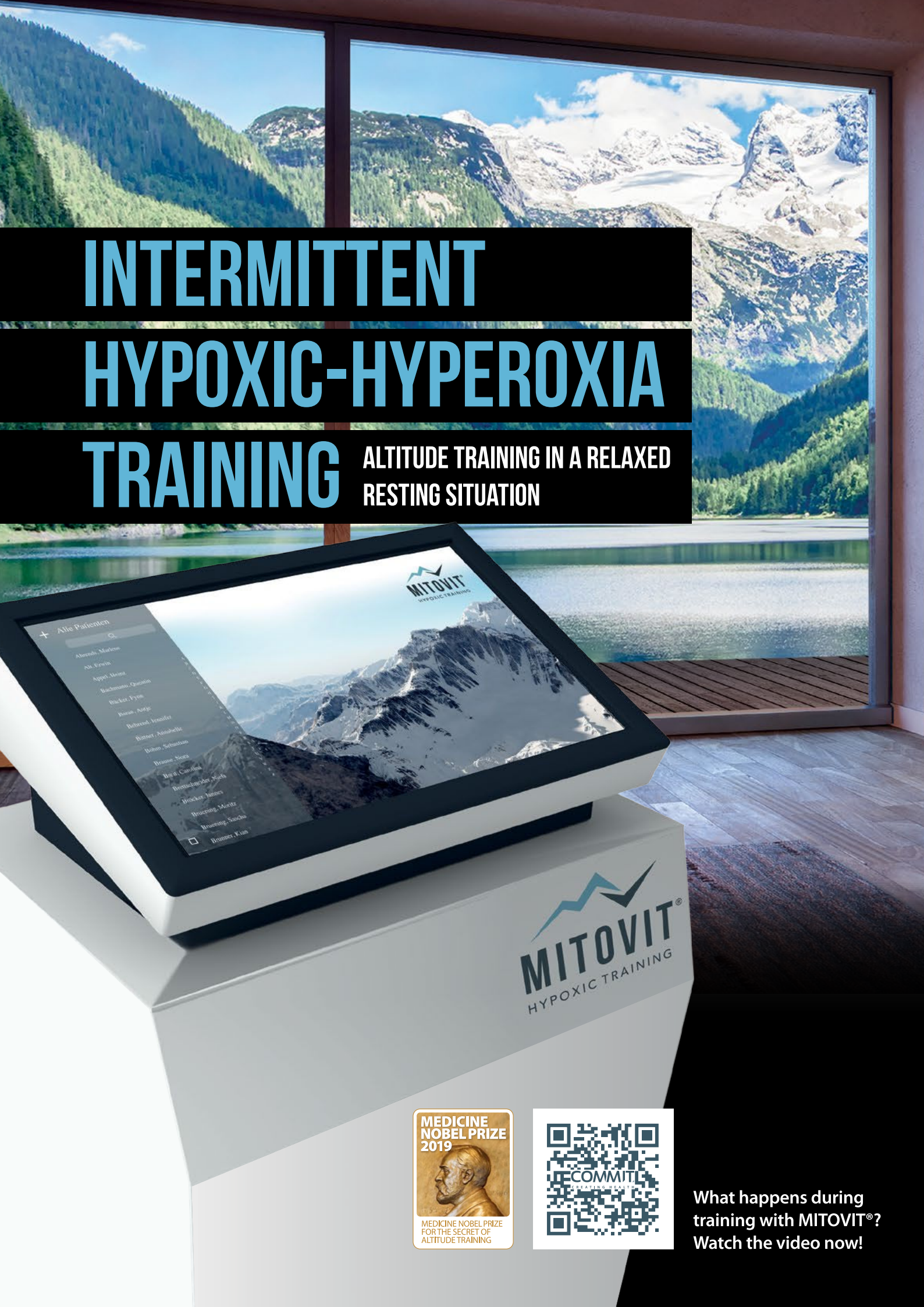
100. Walsh, N.P.; Halson, S.L.; Sargent, C.; Roach, G.D.; Nédélec, M.; Gupta, L.; Leeder, J.; Fullagar, H.H.; Coutts, A.J.; Edwards, B.J.; et al. Sleep and the Athlete: Narrative Review and 2021 Expert Consensus Recommendations. Br J Sports Med 2020, bjsports-2020-102025, doi:10.1136/bjsports-2020-102025.

101. Nédélec, M.; Halson, S.; Abaidia, A.-E.; Ahmaidi, S.; Dupont, G. Stress, Sleep and Recovery in Elite Soccer: A Critical Review of the Literature. Sports Med 2015, 45, 1387–1400, doi:10.1007/s40279-015-0358-z.

102. Fullagar, H.H.K.; Skorski, S.; Duffield, R.; Julian, R.; Bartlett, J.; Meyer, T. Impaired Sleep and Recovery after Night Matches in Elite Football Players. J Sports Sci 2016, 34, 1333–1339, doi:10.1080/02640414.2015.1135249.

103. Swinbourne, R.; Gill, N.; Vaile, J.; Smart, D. Prevalence of Poor Sleep Quality, Sleepiness and Obstructive Sleep Apnoea Risk Factors in Athletes. Eur J Sport Sci 2016, 16, 850–858, doi:10.1080/17461391.2015.1120781.

104. Carriço, S.; Skorski, S.; Duffield, R.; Mendes, B.; Calvete, F.; Meyer, T. Post-Match Sleeping Behavior Based on Match Scheduling over a Season in Elite Football Players. Science and Medicine in Football 2018, 2, 9–15.



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