Orthopädie am St. Lambertiplatz
dr. med robert bethke, MHBA
Facharzt für Orthopädie und Unfallchirurgie, Diplom-Osteopath (DAAO)
Akupunktur · Sportmedizin · Chirotherapie · Notfallmedizin
Osteopathie · Kindermanualtherapie · Funktionelle Medizin

St. Lambertiplatz 6
21335 Lüneburg
Tel. 04131 - 430 31
Fax 04131 - 40 51 00
www.praxis-dr-bethke.de
info@praxis-dr-bethke.de

**Studienauswahl zum Thema**

**Intermittierende Hypoxie-Hyperoxie-Therapie (IHHT)**

**Stand: 20.02.20221**

Veröffentlichung 1[1]:

Intermittent hypoxia research in the former soviet union and the commonwealth of independent States: history and review of the concept and selected applications - PubMed (nih.gov)

In: High Altitude Medicine & Biology. Summer 2002;3(2):205-21. doi: 10.1089/15270290260131939.

„Abstract

This review aims to summarize the basic research in the field of intermittent hypoxia in the Soviet Union and the Commonwealth of Independent States (CIS) **that scientists in other Western countries may not be familiar with**, since Soviet scientists were essentially cut off from the global scientific community for about 60 years. In the 1930s the concept of repeated hypoxic training was developed and the following induction methods were utilized: repeated stays at high-mountain camps for several weeks, regular high altitude flights by plane, training in altitude chambers, and training by inhalation of low-oxygen-gas mixtures. To the present day, intermittent hypoxic training (IHT) has been used extensively for altitude preacclimatization; for the treatment of a variety of clinical disorders, including chronic lung diseases, bronchial asthma, hypertension, diabetes mellitus, Parkinson's disease, emotional disorders, and radiation toxicity, in prophylaxis of certain occupational diseases; and in sports. The basic mechanisms underlying the beneficial effects of IHT are mainly in three areas: regulation of respiration, **free-radical production, and mitochondrial respiration**. It was found that IHT induces increased ventilatory sensitivity to hypoxia, as well as other hypoxia-related physiological changes, such as increased hematopoiesis, alveolar ventilation and lung diffusion capacity, and alterations in the autonomic nervous system. **Due to IHT, antioxidant defense mechanisms are stimulated, cellular membranes become more stable, Ca(2+) elimination from the cytoplasm is increased, and O(2) transport in tissues is improved. IHT induces changes within mitochondria, involving NAD-dependent metabolism, that increase the efficiency of oxygen utilization in ATP production. These effects are mediated partly by NO-dependent reactions.** The marked individual variability both in animals and humans in the response to, and tolerance of, hypoxia is described**. Studies from the Soviet Union and the CIS significantly contributed to the understanding of intermittent hypoxia and its possible beneficial effects** and should stimulate further research in this direction in other countries.“

1 Hinweis: Zu Vereinfachung sind die Abstracts – soweit vorhanden – mitabgedruckt und die Kernaussagen fett-dargestellt.

Veröffentlichung 2:

Moderate hypoxia/hyperoxia attenuates acute hypoxia-induced oxidative damage and improves antioxidant defense in lung mitochondria - PubMed (nih.gov)

In: Acta Physiologica Hungarica. 2012 Dec;99(4):436-46.
doi: 10.1556/APhysiol.99.2012.4.8.

„Abstract

A new mode of adaptive training was explored, which combines periods of hypoxia and hyperoxia (H/H) and is characterized by upregulation of adaptive ROS signals compared to classical intermittent hypoxic training. The purpose of this study was to determine the influence of repetitive moderate sessions of hypoxia and hyperoxia on pro-/antioxidant homeostasis in lung mitochondria of rats exposed to acute severe hypoxia. It was shown that H/H pretreatment [5 cycles of 5 min hypoxia (10% O2 in N2) alternated with 5 min hyperoxia (30% O2 in N2) daily for two weeks] reduced the acute hypoxia-induced basal and stimulated in vitro lipid peroxidation, increased the GSH/GSSG ratio, and decreased the GSSG content. **The enhancement in the level of GSH and activities of MnSOD, GPx and GR in comparison with acute hypoxia as well as the maintenance of GST activity at control level confirm that mitochondrial protection during H/H may be mediated through the modulation of mitochondrial antioxidant levels.** In lung H/H training caused the increase in MnSOD protein synthesis, at the same time, no changes in mRNA MnSOD expression was registered. **This study supports the viewpoint that moderate periodic generation of free radical signal during changes in the oxygen level causes the induction of antioxidant enzyme protein synthesis that may be an important trigger for specific adaptations.**“

Veröffentlichung 3:

(PDF) Moderate intermittent hypoxia/hyperoxia: Implication for correction of mitochondrial dysfunction (researchgate.net)

In: Central European Journal of Biology 7(5), October 2012
DOI: 10.2478/s11535-012-0072-x

„Abstract:

**The purpose of this study was to appreciate the acute hypoxia-induced mitochondrial oxidative damage development and the role of adaptation to hypoxia/hyperoxia (H/H) in correction of mitochondrial dysfunction.** It was demonstrated that long-term sessions of moderate H/H [5 cycles of 5 min hypoxia (10% O2 in N2) alternated with 5 min hyperoxia (30% O2 in N2) daily for two weeks]_attenuated basal and Fe2+/ascorbate-induced lipid peroxidation (LPO) as well as production of carbonyl proteins and H2O2 in liver mitochondria of rats exposed to acute severe hypoxia (7% O2 in N2, 60 min) in comparison with untreated animals. **It was shown that H/H increases the activity of glutathione peroxidase (GPx), reduces hyperactivation of Mn-SOD, and decreases Cu,Zn-SOD activity as compared with untreated rats.** It has been suggested that the induction of Mn-SOD protein expression and the coordinated action of Mn-SOD and GPx could be the mechanisms underlying protective effects of H/H, which promote the correction of the acute hypoxia-induced mitochondrial dysfunction. The increase in Mn-SOD protein synthesis without changes in Mn-SOD

mRNA level under H/H pretreatment indicates that the Mn-SOD activity is most likely dependent on its posttranslational modification or on the redox state of liver mitochondria."

Veröffentlichung 4:

Molecular mechanisms of chronic intermittent hypoxia and hypertension - PubMed (nih.gov)

In: Critical Reviews in Biomedical Engineering. 2012;40(4):265-78. doi: 10.1615/critrevbiomedeng.v40.i4.30.

„Abstract

Obstructive sleep apnea (OSA) is characterized by episodes of repeated airway obstruction resulting in cessation (apnea) or reduction (hypopnea) in airflow during sleep. These events lead to intermittent hypoxia and hypercapnia, sleep fragmentation, and changes in intrathoracic pressure, and are associated with a marked surge in sympathetic activity and an abrupt increase in blood pressure. Blood pressure remains elevated during wakefulness despite the absence of obstructive events resulting in a high prevalence of hypertension in patients with OSA**. There is substantial evidence that suggests that chronic intermittent hypoxia (CIH) leads to sustained sympathoexcitation during the day and changes in vasculature resulting in hypertension in patients with OSA**. Mechanisms of sympathoexcitation include augmentation of peripheral chemoreflex sensitivity and a direct effect on central sites of sympathetic regulation. Interestingly, the vascular changes that occur with CIH have been ascribed to the same molecules that have been implicated in the augmented sympathetic tone in CIH. **This review will discuss the hypothesized molecular mechanisms involved in the development of hypertension with CIH, will build a conceptual model for the development of hypertension following CIH, and will propose a systems biology approach in further elucidating the relationship between CIH and the development of hypertension.**"

Veröffentlichung 5:

HIF-1α Activation by Intermittent Hypoxia Requires NADPH Oxidase Stimulation by Xanthine Oxidase (nih.gov)

In: PLoS One. 2015; 10(3): e0119762. Published online 2015 Mar 9. doi: 10.1371/journal.pone.0119762

„Abstract

Hypoxia-inducible factor 1 (HIF-1) mediates many of the systemic and cellular responses to intermittent hypoxia (IH), which is an experimental model that simulates O2 saturation profiles occurring with recurrent apnea. IH-evoked HIF-1α synthesis and stability are due to increased reactive oxygen species (ROS) generated by NADPH oxidases, especially Nox2. However, the mechanisms by which IH activates Nox2 are not known. We recently reported that IH activates xanthine oxidase (XO) and the resulting increase in ROS elevates intracellular calcium levels. Since Nox2 activation requires increased intracellular calcium levels, we hypothesized XO-mediated calcium signaling contributes to Nox activation by IH. We tested this possibility in rat pheochromocytoma PC12 cells subjected to IH consisting alternating cycles of hypoxia (1.5% O2 for 30 sec) and normoxia (21% O2 for 5 min). Kinetic analysis revealed that IH-induced XO preceded Nox activation. Inhibition of XO activity either by allopurinol or by siRNA prevented IH-induced Nox

activation, translocation of the cytosolic subunits p47phox and p67phox to the plasma membrane and their interaction with gp91phox. ROS generated by XO also contribute to IH-evoked Nox activation via calcium-dependent protein kinase C stimulation. More importantly, silencing XO blocked IH-induced upregulation of HIF-1α demonstrating that HIF-1α activation by IH requires Nox2 activation by XO."

**<u>Anmerkungen:</u> Dies ist eine reine Grundlagenarbeit ohne direkten klinischen Bezug. Allerdings wird die Arbeit aufgeführt, um zu demonstrieren, dass die IHHT Bestandteil universitärer-wissenschaftlicher Forschung ist.**

Veröffentlichung 6:

HIF-1 and ventilatory acclimatization to chronic hypoxia (nih.gov)

In: Respiratory Physiology & Neurobiology. 2008 Dec 10; 164(1-2): 282–287.
doi: 10.1016/j.resp.2008.07.017

„Abstract

Ventilatory acclimatization to hypoxia (VAH) is a time-dependent increase in ventilation and ventilatory O2-sensitivity that involves plasticity in carotid body chemoreceptors and CNS respiratory centers. Hypoxia inducible factor-1α (HIF-1α) controls the expression of several genes that increase physiological O2 supply. Studies using transgenic mice show HIF-1α expression in the carotid bodies and CNS with chronic sustained and intermittent hypoxia is important for VAH. Other O2-sensitive transcription factors such as HIF-2α may be important for VAH by reducing metabolic O2 demands also. Specific gene targets of HIF-1α shown to be involved in VAH include erythropoietin, endothelin-1, neuronal nitric oxide synthase and tyrosine hydroxylase. Other HIF-1α targets that may be involved in VAH include vascular endothelial growth factor, heme oxygenase 1 and cytoglobin. Interactions between these multiple pathways and feedback control of HIF-1α expression from some of the targets support a complex and powerful role for HIF-1α in neural plasticity of physiological control circuits with chronic hypoxia."

**<u>Anmerkungen:</u> Dies ist eine reine Grundlagenarbeit ohne direkten klinischen Bezug. Allerdings wird die Arbeit aufgeführt, um zu demonstrieren, dass die IHHT Bestandteil universitärer-wissenschaftlicher Forschung ist.**

Veröffentlichung 7:

[Adaptation to hypoxia and hyperoxia improves physical endurance: the role of reactive oxygen species and redox-signaling] - PubMed (nih.gov)

In: Ross Fiziol Zh Im I M Sechenova (Russisches Physiologisches Journal mit Namen M. Sechenova). 2012 Jun;98(6):793-807.

„Abstract

We have conducted theoretical foundation, experimental analysis and a pilot study of a new method of adaptation to hypoxia and hyperoxia in the prevention of hypoxic and stress-induced disorders and improving the body's tolerance to physical stress. It has been shown in the experimental part that a combination of physical exercise with adaptation to hypoxia-hyperoxia significantly increased

tolerance to acute physical load (APL) and its active phase. Analysis of lipid peroxidation processes, antioxidant enzymes and HSPs showed that short-term training for physical exercise by itself compensates the stressor, but not the hypoxic component of the APL, the combination of training with adaptation to hypoxia-hyperoxia completely normalizes the stressor and hypoxic components of APL. The pilot study has been performed to evaluate the effectiveness of hypoxic-hyperoxic training course in qualified young athletes with over-training syndrome. After completing the course of hypoxia-hyperoxia adaptation, 14 sessions, accompanied by light mode sports training, the athletes set the normalization of autonomic balance, increased resistance to acute hypoxia in hypoxic test, increased physical performance--increased PWC170, maximal oxygen consumption (VO2max) parameters, their relative values to body mass, diminished shift of rate pressure product in the load. **Thus, we confirmed experimental findings that hypoxic-hyperoxic training optimizes hypoxic (increased athletes resistance to proper hypoxia) and stress (myocardium economy in acute physical stress testing) components in systemic adaptation and restoration of athletes' with over-training syndrome.**"

Veröffentlichung 8:

Intermittent hypoxia training in prediabetes patients: Beneficial effects on glucose homeostasis, hypoxia tolerance and gene expression - PubMed (nih.gov)

In: Experimental Biology and Medicine. 2017 Sep;242(15):1542-1552.
doi: 10.1177/1535370217723578. Epub 2017 Jul 31

„Abstract

The present study aimed at examining beneficial effects of intermittent hypoxia training (IHT) under prediabetic conditions. We investigate the effects of three-week IHT on blood glucose level, tolerance to acute hypoxia, and leukocyte mRNA expression of hypoxia inducible factor 1α (HIF-1α) and its target genes, i.e. insulin receptor, facilitated glucose transporter-solute carrier family-2, and potassium voltage-gated channel subfamily J. Seven healthy and 11 prediabetic men and women (44-70 years of age) were examined before, next day and one month after three-week IHT (3 sessions per week, each session consisting 4 cycles of 5-min 12% O2 and 5-min room air breathing). We found that IHT afforded beneficial effects on glucose homeostasis in patients with prediabetes reducing fasting glucose and during standard oral glucose tolerance test. The most pronounced positive effects were observed at one month after IHT termination. IHT also significantly increased the tolerance to acute hypoxia (i.e. SaO2 level at 20th min of breathing with 12% O2) and improved functional parameters of respiratory and cardiovascular systems. IHT stimulated HIF-1α mRNA expression in blood leukocytes in healthy and prediabetic subjects, but in prediabetes patients the maximum increase was lagged. The greatest changes in mRNA expression of HIF-1α target genes occurred a month after IHT and coincided with the largest decrease in blood glucose levels. The higher expression of HIF-1α was positively associated with higher tolerance to hypoxia and better glucose homeostasis. In conclusion, our results suggest that IHT may be useful for preventing the development of type 2 diabetes. Impact statement The present study investigated the beneficial effects of intermittent hypoxia training (IHT) in humans under prediabetic conditions. **We found that three-week moderate IHT induced higher HIF-1α mRNA expressions as well as its target genes, which were positively correlated with higher tolerance to acute hypoxia and better glucose homeostasis in both middle-aged healthy and prediabetic subjects. This small clinical trial has provided new data suggesting a potential utility of IHT for management of prediabetes patients.**"

Veröffentlichung 9:

The role of hypoxia-inducible factors in oxygen sensing by the carotid body - PubMed (nih.gov)

In: Advances in Experimental Medicine and Biology. 2012;758:1-5.
doi: 10.1007/978-94-007-4584-1_1.

„Abstract

Chronic intermittent hypoxia (IH) associated with sleep-disordered breathing is an important cause of hypertension, which results from carotid body-mediated activation of the sympathetic nervous system. IH triggers increased levels of reactive oxygen species (ROS) in the carotid body, which induce increased synthesis and stability of hypoxia-inducible factor 1α (HIF-1α) and calpain-dependent degradation of HIF-2α. HIF-1 activates transcription of the Nox2 gene, encoding NADPH oxidase 2, which generates superoxide. Loss of HIF-2 activity leads to decreased transcription of the Sod2 gene, encoding manganese superoxide dismutase, which converts superoxide to hydrogen peroxide. Thus, IH disrupts the balance between HIF-1-dependent pro-oxidant and HIF-2-dependent anti-oxidant activities, and this loss of redox homeostasis underlies the pathogenesis of autonomic morbidities associated with IH.“

**Anmerkungen: Dies ist eine reine Grundlagenarbeit ohne direkten klinischen Bezug. Allerdings wird die Arbeit aufgeführt, um zu demonstrieren, dass die IHHT Bestandteil universitärer-wissenschaftlicher Forschung ist.**

Veröffentlichung 10:

Physiological Responses to Two Hypoxic Conditioning Strategies in Healthy Subjects (nih.gov)

In: Frontiers in Physiology. 2016; 7: 675.Published online 2017 Jan 10.
doi: 10.3389/fphys.2016.00675

„Abstract

Objective: Hypoxic exposure can be used as a therapeutic tool by inducing various cardiovascular, neuromuscular, and metabolic adaptations. Hypoxic conditioning strategies have been evaluated in patients with chronic diseases using either sustained (SH) or intermittent (IH) hypoxic sessions. Whether hypoxic conditioning via SH or IH may induce different physiological responses remains to be elucidated.

Methods: Fourteen healthy active subjects (7 females, age 25 ± 8 years, body mass index 21.5 ± 2.5 kg·m−2) performed two interventions in a single blind, randomized cross-over design, starting with either 3 x SH (48 h apart), or 3 x IH (48 h apart), separated by a 2 week washout period. SH sessions consisted of breathing a gas mixture with reduced inspiratory oxygen fraction (FiO2), continuously adjusted to reach arterial oxygen saturations (SpO2) of 70–80% for 1 h. IH sessions consisted of 5 min with reduced FiO2 (SpO2 = 70–80%), followed by 3-min normoxia, repeated seven times. During the first (S1) and third (S3) sessions of each hypoxic intervention, cardiorespiratory parameters, and muscle and pre-frontal cortex oxygenation (near infrared spectroscopy) were assessed continuously.

Results: Minute ventilation increased significantly during IH sessions (+2 ± 2 L·min−1) while heart rate increased during both SH (+11 ± 4 bpm) and IH (+13 ± 5 bpm) sessions. Arterial blood pressure increased during all hypoxic sessions, although baseline normoxic systolic blood

pressure was reduced from S1 to S3 in IH only (−8 ± 11 mmHg). Muscle oxygenation decreased significantly during S3 but not S1, for both hypoxic interventions (S3: SH −6 ± 5%, IH −3 ± 4%); pre-frontal oxygenation decreased in S1 and S3, and to a greater extent in SH vs. IH (−13 ± 3% vs. −6 ± 6%). Heart rate variability indices indicated a significantly larger increase in sympathetic activity in SH vs. IH (lower SDNN, PNN50, and RMSSD values in SH). From S1 to S3, further reduction in heart rate variability was observed in SH (SDNN, PNN50, and RMSSD reduction) while heart rate variability increased in IH (SDNN and RMSSD increase).

Conclusions: **These results showed significant differences in heart rate variability, blood pressure, and tissue oxygenation changes during short-term SH vs. IH conditioning interventions. Heart rate variability may provide useful information about the early adaptations induced by such intervention.**“

Veröffentlichung 11:

The Use of Simulated Altitude Techniques for Beneficial Cardiovascular Health Outcomes in Nonathletic, Sedentary, and Clinical Populations: A Literature Review - PubMed (nih.gov)

In: High Altitude Medicine & Biology. 2017 Dec;18(4):305-321.
doi: 10.1089/ham.2017.0050. Epub 2017 Aug 28.

„Abstract

Lizamore, Catherine A., and Michael J. Hamlin. The use of simulated altitude techniques for beneficial cardiovascular health outcomes in nonathletic, sedentary, and clinical populations: A literature review. High Alt Med Biol 18:305-321, 2017.

Background: The reportedly beneficial improvements in an athlete's physical performance following altitude training may have merit for individuals struggling to meet physical activity guidelines.

Aim: To review the effectiveness of simulated altitude training methodologies at improving cardiovascular health in sedentary and clinical cohorts.

Methods: Articles were selected from Science Direct, PubMed, and Google Scholar databases using a combination of the following search terms anywhere in the article: "intermittent hypoxia," "intermittent hypoxic," "normobaric hypoxia," or "altitude," and a participant descriptor including the following: "sedentary," "untrained," or "inactive."

Results: 1015 articles were returned, of which 26 studies were accepted (4 clinical cohorts, 22 studies used sedentary participants). Simulated altitude methodologies included prolonged hypoxic exposure (PHE: continuous hypoxic interval), intermittent hypoxic exposure (IHE: 5-10 minutes hypoxic:normoxic intervals), and intermittent hypoxic training (IHT: exercising in hypoxia).

Conclusions: In a clinical cohort, PHE for 3-4 hours at 2700-4200 m for 2-3 weeks may improve blood lipid profile, myocardial perfusion, and exercise capacity, while 3 weeks of IHE treatment may improve baroreflex sensitivity and heart rate variability. In the sedentary population, IHE was most likely to improve submaximal exercise tolerance, time to exhaustion, and heart rate variability. Hematological adaptations were unclear. Typically, a 4-week intervention of 1-hour-long PHE intervals 5 days a week, at a fraction of inspired oxygen (FIO2) of 0.15, was beneficial for pulmonary ventilation, submaximal exercise, and maximum oxygen consumption ([Formula: see text]O2max), but an FIO2 of 0.12 reduced hyperemic response and antioxidative capacity. While IHT may be

beneficial for increased lipid metabolism in the short term, it is unlikely to confer any additional advantage over normoxic exercise over the long term. **IHT may improve vascular health and autonomic balance.**"

Veröffentlichung 12:

Limitation of Maximal Heart Rate in Hypoxia: Mechanisms and Clinical Importance (nih.gov)

In: Frontiers in Physiology. 2018; 9: 972.Published online 2018 Jul 23.
doi: 10.3389/fphys.2018.00972

„Abstract

The use of exercise intervention in hypoxia has grown in popularity amongst patients, with encouraging results compared to similar intervention in normoxia. The prescription of exercise for patients largely rely on heart rate recordings (percentage of maximal heart rate (HRmax) or heart rate reserve). It is known that HRmax decreases with high altitude and the duration of the stay (acclimatization). At an altitude typically chosen for training (2,000-3,500 m) conflicting results have been found. Whether or not this decrease exists or not is of importance since the results of previous studies assessing hypoxic training based on HR may be biased due to improper intensity. By pooling the results of 86 studies, this literature review emphasizes that HRmax decreases progressively with increasing hypoxia. The dose–response is roughly linear and starts at a low altitude, but with large inter-study variabilities. Sex or age does not seem to be a major contributor in the HRmax decline with altitude. **Rather, it seems that the greater the reduction in arterial oxygen saturation, the greater the reduction in HRmax, due to an over activity of the parasympathetic nervous system.** Only a few studies reported HRmax at sea/low level and altitude with patients. Altogether, due to very different experimental design, it is difficult to draw firm conclusions in these different clinical categories of people. Hence, forthcoming studies in specific groups of patients are required to properly evaluate (1) the HRmax change during acute hypoxia and the contributing factors, and (2) the physiological and clinical effects of exercise training in hypoxia with adequate prescription of exercise training intensity if based on heart rate."

Veröffentlichung 13:

Basic Biology of Hypoxic Responses Mediated by the Transcription Factor HIFs and Its Implication for Medicine (nih.gov)

In: Biomedicines. 2020 Feb; 8(2): 32.Published online 2020 Feb 13.
doi: 10.3390/biomedicines8020032

„Abstract

Oxygen (O2) is essential for human life. Molecular oxygen is vital for the production of adenosine triphosphate (ATP) in human cells. O2 deficiency leads to a reduction in the energy levels that are required to maintain biological functions. O2 acts as the final acceptor of electrons during oxidative phosphorylation, a series of ATP synthesis reactions that occur in conjunction with the electron transport system in mitochondria. Persistent O2 deficiency may cause death due to malfunctioning biological processes. The above account summarizes the classic view of oxygen. However, this classic view has been reviewed over the last two decades. Although O2 is essential for life, higher organisms such as mammals are unable to biosynthesize molecular O2 in the body. **Because the multiple organs of higher organisms are constantly exposed to the risk of "O2 deficiency," living organisms**

**have evolved elaborate strategies to respond to hypoxia. In this review, I will describe the system that governs oxygen homeostasis in the living body from the point-of-view of the transcription factor hypoxia-inducible factor (HIF).**"

Veröffentlichung 14:

Mechanisms of Cardiovascular Protection Associated with Intermittent Hypobaric Hypoxia Exposure in a Rat Model: Role of Oxidative Stress - PubMed (nih.gov)

In: International Journal of Molecular Sciences. 2018 Jan 26;19(2):366.
doi: 10.3390/ijms19020366.

„Abstract

More than 140 million people live and works (in a chronic or intermittent form) above 2500 m worldwide and 35 million live in the Andean Mountains. Furthermore, in Chile, it is estimated that 55,000 persons work in high altitude shifts, where stays at lowlands and interspersed with working stays at highlands. Acute exposure to high altitude has been shown to induce oxidative stress in healthy human lowlanders, due to an increase in free radical formation and a decrease in antioxidant capacity. However, in animal models, intermittent hypoxia (IH) induce preconditioning, like responses and cardioprotection. Here, we aimed to describe in a rat model the responses on cardiac and vascular function to 4 cycles of intermittent hypobaric hypoxia (IHH). Twelve adult Wistar rats were randomly divided into two equal groups, a four-cycle of IHH, and a normobaric hypoxic control. Intermittent hypoxia was induced in a hypobaric chamber in four continuous cycles (1 cycle = 4 days hypoxia + 4 days normoxia), reaching a barometric pressure equivalent to 4600 m of altitude (428 Torr). At the end of the first and fourth cycle, cardiac structural, and functional variables were determined by echocardiography. Thereafter, ex vivo vascular function and biomechanical properties were determined in femoral arteries by wire myography. We further measured cardiac oxidative stress biomarkers (4-Hydroxy-nonenal, HNE; nytrotirosine, NT), reactive oxygen species (ROS) sources (NADPH and mitochondrial), and antioxidant enzymes activity (catalase, CAT; glutathione peroxidase, GPx, and superoxide dismutase, SOD). Our results show a higher ejection and shortening fraction of the left ventricle function by the end of the 4th cycle. Further, femoral vessels showed an improvement of vasodilator capacity and diminished stiffening. Cardiac tissue presented a higher expression of antioxidant enzymes and mitochondrial ROS formation in IHH, as compared with normobaric hypoxic controls. IHH exposure determines a preconditioning effect on the heart and femoral artery, both at structural and functional levels, associated with the induction of antioxidant defence mechanisms. However, mitochondrial ROS generation was increased in cardiac tissue. **These findings suggest that initial states of IHH are beneficial for cardiovascular function and protection.“**

Veröffentlichung 15:

Intermittent hypoxia: a low-risk research tool with therapeutic value in humans - PubMed (nih.gov)

In: Journal of Applied Physiology (1985). 2015 Mar 1;118(5):520-32.
doi: 10.1152/japplphysiol.00564.2014. Epub 2014 Dec 30.

„Abstract

Intermittent hypoxia has generally been perceived as a high-risk stimulus, particularly in the field of sleep medicine, because it is thought to initiate detrimental cardiovascular, respiratory, cognitive, and metabolic outcomes. In contrast, the link between intermittent hypoxia and beneficial outcomes has received less attention, perhaps because it is not universally understood that outcome measures following exposure to intermittent hypoxia may be linked to the administered dose**. The present review is designed to emphasize the less recognized beneficial outcomes associated with intermittent hypoxia. The review will consider the role intermittent hypoxia has in cardiovascular and autonomic adaptations, respiratory motor plasticity, and cognitive function.** Each section will highlight the literature that contributed to the belief that intermittent hypoxia leads primarily to detrimental outcomes. The second segment of each section will consider the possible risks associated with experimentally rather than naturally induced intermittent hypoxia. Finally, the body of literature indicating that intermittent hypoxia initiates primarily beneficial outcomes will be considered. The overarching theme of the review is that the use of intermittent hypoxia in research investigations, coupled with reasonable safeguards, should be encouraged because of the potential benefits linked to the administration of a variety of low-risk intermittent hypoxia protocols."

Veröffentlichung 16:

Intermittent hypoxia in childhood: the harmful consequences versus potential benefits of therapeutic uses - PubMed (nih.gov)

In: Frontiers in Pediatrics. 2015 May 19;3:44.
doi: 10.3389/fped.2015.00044. eCollection 2015.

„Abstract

Intermittent hypoxia (IH) often occurs in early infancy in both preterm and term infants and especially at 36-44 weeks postmenstrual age. These episodes of IH could result from sleep-disordered breathing or may be temporally unrelated to apnea or bradycardia events. There are numerous reports indicating adverse effects of IH on development, behavior, academic achievement, and cognition in children with sleep apnea syndrome. It remains uncertain about the exact causative relationship between the neurocognitive and behavioral morbidities and IH and/or its associated sleep fragmentation. On the other hand, well-controlled and moderate IH conditioning/training has been used in sick children for treating their various forms of bronchial asthma, allergic dermatoses, autoimmune thyroiditis, cerebral palsy, and obesity. **This review article provides an updated and impartial analysis on the currently available evidence in supporting either side of the seemingly contradictory scenarios. We wish to stimulate a comprehensive understanding of such a complex physiological phenomenon as intermittent hypoxia, which may be accompanied by other confounding factors (e.g., hypercapnia, polycythemia), in order to prevent or reduce its harmful consequences, while maximizing its potential utility as an effective therapeutic tool in pediatric patients**."

Veröffentlichung 17:

Intermittent hypoxia in childhood: the harmful consequences versus potential benefits of therapeutic uses - PubMed (nih.gov)

In: Frontiers in Pediatrics. 2015 May 19;3:44.
doi: 10.3389/fped.2015.00044. eCollection 2015.

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Intermittent hypoxia (IH) often occurs in early infancy in both preterm and term infants and especially at 36-44 weeks postmenstrual age. These episodes of IH could result from sleep-disordered breathing or may be temporally unrelated to apnea or bradycardia events. There are numerous reports indicating adverse effects of IH on development, behavior, academic achievement, and cognition in children with sleep apnea syndrome. It remains uncertain about the exact causative relationship between the neurocognitive and behavioral morbidities and IH and/or its associated sleep fragmentation. On the other hand, well-controlled and moderate IH conditioning/training has been used in sick children for treating their various forms of bronchial asthma, allergic dermatoses, autoimmune thyroiditis, cerebral palsy, and obesity. **This review article provides an updated and impartial analysis on the currently available evidence in supporting either side of the seemingly contradictory scenarios. We wish to stimulate a comprehensive understanding of such a complex physiological phenomenon as intermittent hypoxia, which may be accompanied by other confounding factors (e.g., hypercapnia, polycythemia), in order to prevent or reduce its harmful consequences, while maximizing its potential utility as an effective therapeutic tool in pediatric patients**."

Veröffentlichung 18:

(PDF) Mitochondria as a Target of Intermittent Hypoxia (researchgate.net)

In: International Journal of Physiology and Pathophysiology 6(4):347-362, January 2015
DOI: 10.1615/IntJPhysPathophys.v6.i4.90

„Abstract

Mitochondria as a Target of Intermittent Hypoxia Iryna M. Mankovska & Tetyana V. Serebrovska* Bogomolets Institute of Physiology, National Academy of Sciences of Ukraine, Kyiv, Ukraine * Address all correspondence to Tetyana V. Serebrovska, e-mail: sereb@biph.kiev.ua ABSTRACT: The review is focused upon summarizing the current knowledge of the mechanisms of interval hypoxic training (IHT) impact on the mitochondria (Mt) structure and functions in comparison with the effects of acute hypoxia (AH). It has been revealed that AH causes mitochondrial swelling, vacuolization of organelles, disorganization and destruction of mitochondrial membranes. When exposed to IHT, the increase in the total number of mitochondria, the reduction of the number of structurally modified organelles, the appearance of energetically active Mt with vesicular cristae, and the micromitochondria (microMt) formation are observed. One of the key mechanisms of cell damage during hypoxia and reoxygenation is excessive production of reactive oxygen species (ROS) in the mitochondria which oxidize proteins, lipids and DNA. On the other hand, low level of ROS production is protective and serves as a trigger for adaptive responses. IHT leads to reprogramming of the mitochondria metabolism, ensuring adequate production of ATP. The activation of potassium transport in the mitochondrial matrix under IHT is a protective mechanism against Ca2+ overload caused by acute hypoxia. The intensity of neuronal mitochondrial energy production in the brain stem is directly related to the regulation of neurotransmitter metabolism, including glutamate and GABA, which are involved in the mechanisms of respiratory rhythmogenesis formation. All adaptive reactions to hypoxia are regulated by HIF-factors (HIF-1, HIF-2, HIF-3). Each of HIF-subunits plays a certain role depending on the mode of hypoxia-induced stress. These peculiarities can be important when choosing a mode of IHT to prevent and treat various diseases. **New data on the organ**

**specificity of HIF operation provide potential pharmacological regulation of HIFs as a new therapeutic approach for treatment of diseases.**“

Veröffentlichung 19:

Effect of intermittent hypoxia on pro- and antioxidant balance in rat heart during high-intensity chronic exercise - PubMed (nih.gov)

In: Acta Physiologica Hungarica. 2005 Dec;92(3-4):211-220.
doi: 10.1556/APhysiol.92.2005.3-4.3.

„Abstract

The purpose of the present study was to elucidate the influence of sessions of intermittent hypoxic training (IHT) alone and in combination with high-intensity chronic exercise on lipid peroxidation and antioxidative defense system in rat heart. High-intensity chronic exercise was performed as swimming training with load that corresponded to ~ 75% VO2max(30 min/day, 5 days/wk, for 4 wk). IHT consisted of repeated episodes of hypoxia (12% O2, 15 min), interrupted by equal periods of recovery (5 sessions/day, for 2wk). Sessions of IHT were applied during the first two weeks and during the last two weeks of chronic exercise. It was shown that long-term training was accompanied by the accumulation of thiobarbituric acid reactive substances (TBARS) in myocardium. IHT attenuated the increase in TBARS content caused by high-intensity chronic exercise and it enhanced myocardial reduced glutathione concentration, activities of superoxide dismutase, catalase, and glutathione peroxidase in comparison with trained animals only. No significant changes were found in glutathione reductase, glucose-6-phosphate dehydrogenase activities. **Our results suggest that intermittent hypoxic stimuli may induce a state of preconditioning that protects the heart from oxidative stress evoked by high-intensity chronic exercise.**“

Veröffentlichung 20:

Interval hypoxic training improves autonomic cardiovascular and respiratory control in patients with mild chronic obstructive pulmonary disease - PubMed (nih.gov)

In: Journal of Hypertension. 2009 Aug;27(8):1648-54. doi: 10.1097/HJH.0b013e32832c0018.

„Abstract

Objectives: Chronic obstructive pulmonary disease (COPD) is associated with cardiac autonomic nervous system dysregulation. This study evaluates the effects of interval hypoxic training on cardiovascular and respiratory control in patients with mild COPD.

Methods: In 18 eucapnic normoxic mild COPD patients (age 51.7 +/- 2.4 years, mean +/- SEM), randomly assigned to either training or placebo group, and 14 age-matched healthy controls (47.7 +/- 2.8 years), we monitored end-tidal carbon dioxide, airway flow, arterial oxygen saturation, electrocardiogram, and continuous noninvasive blood pressure at rest, during progressive hypercapnic hyperoxia and isocapnic hypoxia to compare baroreflex sensitivity to hypoxia and hypercapnia before and after 3 weeks of hypoxic training. In double-blind fashion, both groups received 15 sessions of passive intermittent hypoxia (training group) or normoxia (placebo group). For the hypoxia group, each session consisted of three to five hypoxic (15-12% oxygen) periods (3-5 min) with 3-min normoxic intervals. The placebo group inhaled normoxic air.

Results: Before training, COPD patients showed depressed baroreflex sensitivity, as compared with healthy individuals, without evident chemoreflex abnormalities. After training, in contrast to placebo group, the training group showed increased ($P < 0.05$) baroreflex sensitivity up to normal levels and selectively increased hypercapnic ventilatory response ($P < 0.05$), without changes in hypoxic ventilatory response.

Conclusion: Eucapnic normoxic mild COPD patients already showed signs of cardiovascular autonomic abnormalities at baseline, **which normalized with hypoxic training**. If confirmed in more severe patients, **interval hypoxic training may be a therapeutic strategy to rebalance early autonomic dysfunction in COPD patients.**"

Veröffentlichung 21:

Effects of intermittent hypoxic training on orthostatic reactions of the cardiorespiratory system - PubMed (nih.gov)

In: Bulletin of Experimental Biology and Medicine. 2008 Jun;145(6):661-4.
doi: 10.1007/s10517-008-0182-7.

„Abstract

The possibility of using intermittent hypoxic training for stimulation of physiological mechanisms underlying the compensatory hemodynamic reactions to orthostatic load was studied in animal experiments. Intermittent hypoxic training had a favorable impact on circulatory reactions, which manifested in stabilization of blood pressure and heart filling pressure and in a decrease in orthostatic hypotension during the initial period of orthostasis. We hypothesized that the positive effect of intermittent hypoxic training on the correction of negative hemodynamic shifts is determined by the training effect aimed at the increase in the vascular tone and venous return to the heart. **These results can serve as validation for preventive use of intermittent hypoxic training for reducing blood draining in the lower part of the body, correction of the compensatory orthostatic reaction of the circulatory system, and hence, for improvement of orthostatic resistance.**"

Veröffentlichung 22:

Role of intermittent hypoxia in the treatment of bronchial asthma and chronic obstructive pulmonary disease - PubMed (nih.gov)

In: Current Opinion in Allergy and Clinical Immunology. 2010 Jun;10(3):206-13.
doi: 10.1097/ACI.0b013e32833903a6.

„Abstract

Purpose of review: The purpose of this review is to describe the impact that exposure to intermittent hypoxic training (IHT) could have on bronchial asthma and chronic obstructive pulmonary disease (COPD). This is of particular interest, as an increasing number of patients suffer from severe symptoms of bronchial asthma and COPD and desire more effective and efficient treatment options with fewer side effects.

Recent findings: Exposure to IHT has been shown to raise baroreflex sensitivity to normal levels and to selectively increase hypercapnic ventilatory response, total exercise time, total haemoglobin mass,

and lung diffusion capacity for carbon monoxide in COPD patients. However, evidence proving that IHT leads to health benefit effects in bronchial asthma patients has not been produced by recent literature.

Summary: **Recent research outlines the value of IHT as a therapeutic strategy for the treatment of COPD patients, leading to more efficient ventilation. Additionally, IHT might represent an attractive method to complement the known beneficial effects of exercise training and to rebalance early autonomic dysfunction in COPD patients.** Future research examining the potential risks and benefits of IHT could pave the way for the development of new therapeutic approaches for patients suffering from bronchial asthma and COPD."

Veröffentlichung 23:

Effect of hypoxic training on inflammatory and metabolic risk factors: a crossover study in healthy subjects (nih.gov)

In: Physiological Reports. 2014 Jan 1; 2(1): e00198. Published online 2014 Jan 13.
doi: 10.1002/phy2.198

„Abstract

The purpose of this study was to investigate the influence of hypoxic physical exercise on metabolic syndrome (MS) risk markers and high-sensitivity C-reactive protein (CRP) and to compare its effects on preperitoneal fat, arterial stiffness, and several blood parameters related to MS to those of a control group who trained under normoxic conditions. Fourteen healthy men were examined. Participants performed treadmill exercise 3 days per week for 4 weeks, under either normobaric hypoxic or normobaric normoxic conditions, for 50 min (including a 5-min warm-up and 5-min cool down) after a 30-min rest period. Exercise was performed at a heart rate (HR) corresponding to 60% of the HR at each individual's maximum oxygen uptake. Training under the different environmental conditions was performed 4 months apart to ensure a sufficient washout period. Waist circumference, preperitoneal fat thickness, brachial-ankle pulse wave velocity, and high-sensitivity CRP after training were significantly lower in the hypoxic group than in the normoxic group. **Our results suggest that regular short-term hypoxic training may more effectively reduce arterial stiffness, and thus prevent arteriosclerosis, compared to training performed at a similar exercise intensity under normoxic conditions."**

Veröffentlichung 24:

НОВЫЙ ПОДХОД В ТАКТИКЕ ЛЕЧЕНИЯ СУБКЛИНИЧЕСКОГО ГИПЕРТИРЕОЗА - Фундаментальные исследования (научный журнал) (fundamental-research.ru)

Übersetzung: „A NEW APPROACH IN TREATMENT STRATEGY OF SUBCLINICAL HYPERTHYROIDISM"

In: Фундаментальные исследования. – 2013. – № 3 (часть 1) – С. 13-16 (Fundamental research Nr. 3, 2013)
DOI 615.835.14.03: 616.441-02

„Abstract:

The changes in the immune status in patients with subclinical hyperthyroidism was identifi ed. Efficiency of normobaric interval hypoxic training in treatment of subclinical hyperthyroidism was shown. After hypoxic therapy it was observed positive changes in immune status as increasing the number of CD3+ and CD8+ -cells, reducing CD4+ -cells, normalized immunoregulatory index. In the study of humoral immunity the normalization of the content of general B-lymphocytes and serum IgA, IgM, IgG, the reduction of circulating immune complexes and antibodies to receptor of pituitary thyroid-stimulating hormone. All this has led to the recovery of thyroid function, demonstrated in the normalization of blood level of pituitary thyroid-stimulating hormone. **Interval hypoxic training may be recommended as monotherapy in subclinical hyperthyroidism to prevent the manifestation of the disease in clinically significant form.**"

Veröffentlichung 25:

ТЕРМОДИНАМИЧЕСКИЕ МЕХАНИЗМЫ ПРОТЕКЦИИ МОЗГА ОТ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ ИМПУЛЬСНО-ГИПОКСИЧЕСКИМИ АДАПТАЦИЯМИ - Успехи современного естествознания (научный журнал) (natural-sciences.ru)

Übersetzung: THERMODYNAMISCHE MECHANISMEN VON BRAIN PROTECTION VON MALIGNANT TUMORS PULSE-HYPOXIC ADAPTATIONS

In: Advances in current natural sciences. – 2012. – № 1 – P. 41-44

„Abstract:

**The fact of protective influence new bionics a regime of a mode impulse hypoxia of adaptations on rehabilitationsprocesses cerebral cortex after distance inside cranium of tumors at neurosurgical of the patients is established**. The mechanism of the protection of a brain from a relapse of malignant tumors can be the coordination of rhythms energoproduction and energoconsume during formation of adaptation."

Veröffentlichung 26:

NON-DRUG TREATMENT FOR ARTERIAL HYPOTONIA IN PREGNANT WOMEN | | Pacific Medical Journal (tmj-vgmu.ru)

In: Pacific Medical Journal, 2010, No. 2, p. 106–107.
DOI: 611-013.16: 618.31

„Abstract

The authors analyze effect of normobaric hypoxytherapy on the gestation course and act of delivery while observing 78 women with arterial hypotonia. **The two-week course of the hypoxytherapy against the traditional treatment** administered on the 24-26 gestation weeks considerably decreased the risk of gestational toxicosis and frequency of premature labour. **The paper discusses the mechanism of how the procedure acts upon lipid peroxygenation, anti-oxidative system activity, lipid metabolism, and uterine, fetal and placental circulation.**"

Veröffentlichung 27:

Induction of tumor arrest and differentiation with prolonged survival by intermittent hypoxia in a mouse model of acute myeloid leukemia - PubMed (nih.gov)

In: Blood. 2006 Jan 15;107(2):698-707.
doi: 10.1182/blood-2005-03-1278. Epub 2005 Sep 15.

„Abstract

We showed previously that mild real hypoxia and hypoxia-mimetic agents induced in vitro cell differentiation of acute myeloid leukemia (AML). We here investigate the in vivo effects of intermittent hypoxia on syngenic grafts of leukemic blasts in a PML-RARalpha transgenic mouse model of AML. For intermittent hypoxia, leukemic mice were housed in a hypoxia chamber equivalent to an altitude of 6000 m for 18 hours every consecutive day. **The results show that intermittent hypoxia significantly prolongs the survival of the leukemic mice that received transplants, although it fails to cure the disease. By histologic and cytologic analyses, intermittent hypoxia is shown to inhibit the infiltration of leukemic blasts in peripheral blood, bone marrow, spleen, and liver without apoptosis induction. More intriguingly, intermittent hypoxia also induces leukemic cells to undergo differentiation with progressive increase of hypoxia-inducible factor-1alpha protein, as evidenced by morphologic criteria of maturating myeloid cells and increased expression of mouse myeloid cell differentiation-related antigens Gr-1 and Mac-1.** Taken together, this study represents the first attempt to characterize the in vivo effects of hypoxia on an AML mouse model. Additional investigations may uncover ways to mimic the differentiative effects of hypoxia in a manner that will benefit human patients with AML.“

Veröffentlichung 28:

Hypoxic conditioning and the central nervous system: A new therapeutic opportunity for brain and spinal cord injuries? (nih.gov)

In: Experimental Biology and Medicine (Maywood). 2017 Jun; 242(11): 1198–1206.Published online 2017 Jun 6.
doi: 10.1177/1535370217712691

„Abstract

Central nervous system diseases are among the most disabling in the world. Neuroprotection and brain recovery from either acute or chronic neurodegeneration still represent a challenge in neurology and neurorehabilitation as pharmacology treatments are often insufficiently effective. **Conditioning the central nervous system has been proposed as a potential non-pharmacological neuro-therapeutic.** Conditioning refers to a procedure by which a potentially deleterious stimulus is applied near to but below the threshold of damage to the organism to increase resistance to the same or even different noxious stimuli given above the threshold of damage. Hypoxic conditioning has been investigated in several cellular and preclinical models and is now recognized as inducing endogenous mechanisms of neuroprotection. **Ischemic, traumatic, or chronic neurodegenerative diseases can benefit from hypoxic conditioning strategies aiming at preventing the deleterious consequences or reducing the severity of the pathological condition (preconditioning) or aiming at inducing neuroplasticity and recovery (postconditioning) following central nervous system injury.** Hypoxic conditioning can consist in single (sustained) or cyclical (intermittent, interspersed by short period of normoxia) hypoxia stimuli which duration range from few minutes to several hours and

that can be repeated over several days or weeks. This mini-review addresses the existing evidence regarding the use of hypoxic conditioning as a potential innovating neuro-therapeutic modality to induce neuroprotection, neuroplasticity and brain recovery. This mini-review also emphasizes issues which remain to be clarified and future researches to be performed in the field."

Veröffentlichung 29:

Intermittent hypoxic-hyperoxic training on cognitive performance in geriatric patients - PubMed (nih.gov)

In: Alzheimers & Dementia (N Y). 2017 Feb 8;3(1):114-122.
doi: 10.1016/j.trci.2017.01.002. eCollection 2017 Jan.

„Abstract

Introduction: Intermittent hypoxic-hyperoxic training (IHHT) may complement a multimodal training intervention (MTI) for improving cognitive function and exercise tolerance in geriatric patients.

Methods: Thirty-four patients (64-92 years) participated in this randomized controlled trial. Before and after the 5- to 7-week intervention period (MTI + IHHT vs. MTI + ambient air), cognitive function was assessed by the Dementia-Detection Test (DemTect) and the Sunderland Clock-Drawing Test (CDT), and functional exercise capacity by the total distance of the 6-Minute Walk Test (6MWT).

Results: DemTect and CDT indicated significantly larger improvements after MTI + IHHT (+16.7% vs. -0.39%, P < .001) and (+10.7% vs. -8%, P = .031) which was also true for the 6MWT (+24.1% vs. +10.8%, P = .021).

Discussion: **IHHT turned out to be easily applicable to and well tolerated by geriatric patients up to 92 years. IHHT contributed significantly to improvements in cognitive function and functional exercise capacity in geriatric patients performing MTI**."

Veröffentlichung 30:

(PDF) Mitochondria as a Target of Intermittent Hypoxia (researchgate.net)

In: International Journal of Physiology and Pathophysiology 6(4):347-362, January 2015
DOI: 10.1615/IntJPhysPathophys.v6.i4.90

„ABSTRACT: The review is focused upon summarizing the current knowledge of the mechanisms of interval hypoxic training (IHT) impact on the mitochondria (Mt) structure and functions in comparison with the effects of acute hypoxia (AH). It has been revealed that AH causes mitochondrial swelling, vacuolization of organelles, disorganization and destruction of mitochondrial membranes. **When exposed to IHT, the increase in the total number of mitochondria, the reduction of the number of structurally modified organelles, the appearance of energetically active Mt with vesicular cristae, and the micromitochondria (microMt) formation are observed. One of the key mechanisms of cell damage during hypoxia and reoxygenation is excessive production of reactive oxygen species (ROS) in the mitochondria which oxidize proteins, lipids and DNA. On the other hand, low level of ROS production is protective and serves as a trigger for adaptive responses. IHT leads to reprogramming of the mitochondria metabolism, ensuring adequate production of ATP.** The activation of potassium transport in the mitochondrial matrix

under IHT is a protective mechanism against Ca2+ overload caused by acute hypoxia. **The intensity of neuronal mitochondrial energy production in the brain stem is directly related to the regulation of neurotransmitter metabolism, including glutamate and GABA, which are involved in the mechanisms of respiratory rhythmogenesis formation. All adaptive reactions to hypoxia are regulated by HIF-factors (HIF-1, HIF-2, HIF-3).** Each of HIF-subunits plays a certain role depending on the mode of hypoxia-induced stress. These peculiarities can be important when choosing a mode of IHT to prevent and treat various diseases. **New data on the organ specificity of HIF operation provide potential pharmacological regulation of HIFs as a new therapeutic approach for treatment of diseases.**"

Veröffentlichung 31:

Intermittent Hypoxia and Health: From Evolutionary Aspects to Mitochondria Rejuvenation (researchgate.net)

In: L. Xi, T.V. Serebrovskaya (eds.), Intermittent Hypoxia and Human Diseases, 253
DOI 10.1007/978-1-4471-2906-6_21, © Springer-Verlag London 2012

„Abstract

Mitochondrial aging manifests as gradual depletion of energy reserves at cellular and systemic levels, as well as lowered stress resistance. Vital functional state of mitochondria is essential to reduce burden of age-dependent degenerative diseases and prolong health span. Two mitochondria-rejuvenating interventions: intermittent hypoxic training (IHT) and extended morning fasting (EMF), as engineered derivates of naturally occurred intermittent oxygen restriction (IOR) and intermittent calorie restriction (ICR), have been already in clinical practice. IHT and EMF utilize the familiar developmental and adaptational genetic programs, evolutionarily "preinstalled" in all aerobic organisms. Both ICR and IOR employ a common mitochondria-rejuvenating pathway, the mitoptosis – a selective elimination of the mitochondria that excessively produce reactive oxygen species in the cells. Mitoptosis is a natural process that maintains quality of mitochondria in the female germinal cells during early embryogenesis and can be stimulated and maintained by IOR and ICR also in postmitotic cells of adult organisms. ICR and IOR synergistically diminish the basal level of mitochondria-dependent oxidative stress that is supposed to be the key factor modulating life span and health span in aerobes. Furthermore, ICR and IOR in fl uence longevity and tempo of development of age-related diseases via several mitochondria-independent pathways, such as suppressed protein glycation, enhanced DNA repair, accelerated protein turnover, stimulation of erythropoetin, growth hormone, heat shock protein 70, and other functional proteins. In addition, the IOR speci fi cally intensi fi es stem cells-dependent tissue repair**. The synergistic application of IOR- and ICR-based protocols, accompanied by nutrigenomical adjustment and individualized nutraceutical supplementation, brings multiple health bene fi ts and alleviation or cure in numerous chronic degenerative and agerelated diseases.** Further development of engineered ICR and IOR protocols should help their advanced clinical implementation and user-friendly, self-help applications."

Veröffentlichung 32:

INTRAVENOUS LASERTHERAPY AND INTERVAL NORMOBARIC HYPOXYTHERAPY EFFECTIVENESS IN ASTHMA AND COMORBID ESSENTIAL HYPERTENSION COMPLEX THERAPY | Uryasev | I.P. Pavlov Russian Medical Biological Herald (eco-vector.com)

Bibliographische Daten auf der Seite

„Abstract: 82 patients with asthma and comorbid essential hypertension were examined with the aim of intravenous lasertherapy and interval normobaric hypoxytherapy evaluation in combined pathology complex therapy. Physical factors including in therapy of patients with this combined pathology definitely improves condition and functional indexes; positive dynamics expression also might help drugs dose decreasing. **It allows recommend intravenous lasertherapy and interval normobaric hypoxytherapy adding to basic medicinal therapy**."

Veröffentlichung 33:

Fitness and therapeutic potential of intermittent hypoxia training: a matter of dose - PubMed (nih.gov)

In: Fiziol Zh (Physiologisches Journal). 2016;62(3):78-91.
doi: 10.15407/fz62.03.078.

„Abstract

The introduction of different methods of intermittent hypoxic training (IHT) into fitness, sports, military and medical practice has raised a lot of questions about the most beneficial regimens of such treatment and their optimal instrumental implementation. Low doses of hypoxia might not be sufficient stimuli to mobilize adaptive mechanisms, while severe or prolonged hypoxia may provoke dangerous pathological processes. In this review, we pay attention to narrow practical question of the most effective and convenient technology of IHT implementation, notably the inhalation of hypoxic gas mixtures. Data strongly suggest that in humans the training with 15-13% inhaled oxygen (FiO2) at various time characteristics does not provide marked positive changes. **Short-term daily sessions consisting 3-4 bouts of 5-7 min exposures to 12-10% FiO2 alternating with equal durations of normoxia for 2-3 weeks have been shown as a most beneficial without maladaptive consequences for fitness and treatment of some diseases.** More severe or longer intermittent hypoxia protocols must be accompanied by strict monitoring of blood oxygen saturation (SpO2), electrocardiogram, breathing pattern and arterial blood pressure in order to avoid unexpected undesirable individual reactions. For sports purposes, the reduction of oxygen content to individually tolerable level for some minutes is justified as far as it maximizes benefits. However, such regimen requires preliminary diagnostics of individual hypoxic tolerance and cardio-respiratory reactivity as well as rigorous monitoring of vital functions during IHT and good feedback device. The use of oxygen concentrations below 12% for treatment of diseases, especially in children and the elderly, are required substantial additional research. Recently, a new mode of adaptive training was explored, which combines periods of hypoxia (12-10% FiO2) and hyperoxia (30-35% FiO2). Limited evidences suggest that such regime can reduce the time of recovery periods, that is shorten the duration of sessions. However, there is still no strong comparative evidence for humans that this method is much more efficient than hypoxic-normoxic mode. We appeal to all scientists working in the field of IHT not to hide their negative results but publish all observations in the open press. It will make a significant contribution in developing of common guidelines for IHT implementation to improve public health of our Planet."

Veröffentlichung 34:

Intermittent Hypoxia-Hyperoxia Training Improves Cognitive Function and Decreases Circulating Biomarkers of Alzheimer's Disease in Patients with Mild Cognitive Impairment: A Pilot Study (nih.gov)

In: International Journal of Molecular Sciences. 2019 Nov; 20(21): 5405.Published online 2019 Oct 30.

doi: 10.3390/ijms20215405

„Abstract

Alzheimer's disease (AD) affects not only the central nervous system, but also peripheral blood cells including neutrophils and platelets, which actively participate in pathogenesis of AD through a vicious cycle between platelets aggregation and production of excessive amyloid beta (Aβ). Platelets adhesion on amyloid plaques also increases the risk of cerebral microcirculation disorders. Moreover, activated platelets release soluble adhesion molecules that cause migration, adhesion/activation of neutrophils and formation of neutrophil extracellular traps (NETs), which may damage blood brain barrier and destroy brain parenchyma. The present study examined the effects of intermittent hypoxic-hyperoxic training (IHHT) on elderly patients with mild cognitive impairment (MCI), a precursor of AD. Twenty-one participants (age 51–74 years) were divided into three groups: Healthy Control (n = 7), MCI+Sham (n = 6), and MCI+IHHT (n = 8). IHHT was carried out five times per week for three weeks (total 15 sessions). Each IHHT session consisted of four cycles of 5-min hypoxia (12% FIO2) and 3-min hyperoxia (33% FIO2). Cognitive parameters, Aβ and amyloid precursor protein (APP) expression, microRNA 29, and long non-coding RNA in isolated platelets as well as NETs in peripheral blood were investigated. We found an initial decline in cognitive function indices in both MCI+Sham and MCI+IHHT groups and significant correlations between cognitive test scores and the levels of circulating biomarkers of AD. Whereas sham training led to no change in these parameters, IHHT resulted in the improvement in cognitive test scores, along with significant increase in APP ratio and decrease in Aβ expression and NETs formation one day after the end of three-week IHHT. Such effects on Aβ expression and NETs formation remained more pronounced one month after IHHT. **In conclusion, our results from this pilot study suggested a potential utility of IHHT as a new non-pharmacological therapy to improve cognitive function in pre-AD patients and slow down the development of AD.**“

Veröffentlichung 35:

Therapeutic potential of intermittent hypoxia: a matter of dose - PubMed (nih.gov)

In: American journal of physiology. Regulatory, integrative and comparative physiology. 2014 Nov 15;307(10):R1181-97.
doi: 10.1152/ajpregu.00208.2014. Epub 2014 Sep 17.

„Abstract

Intermittent hypoxia (IH) has been the subject of considerable research in recent years, and triggers a bewildering array of both detrimental and beneficial effects in multiple physiological systems. Here, we review the extensive literature concerning IH and its impact on the respiratory, cardiovascular, immune, metabolic, bone, and nervous systems. One major goal is to define relevant IH characteristics leading to safe, protective, and/or therapeutic effects vs. pathogenesis. To understand the impact of IH, it is essential to define critical characteristics of the IH protocol under investigation, including potentially the severity of hypoxia within episodes, the duration of hypoxic episodes, the number of hypoxic episodes per day, the pattern of presentation across time (e.g., within vs. consecutive vs. alternating days), and the cumulative time of exposure. Not

surprisingly, severe/chronic IH protocols tend to be pathogenic, whereas any beneficial effects are more likely to arise from modest/acute IH exposures. Features of the IH protocol most highly associated with beneficial vs. pathogenic outcomes include the level of hypoxemia within episodes and the number of episodes per day. Modest hypoxia (9-16% inspired O2) and low cycle numbers (3-15 episodes per day) most often lead to beneficial effects without pathology, whereas severe hypoxia (2-8% inspired O2) and more episodes per day (48-2,400 episodes/day) elicit progressively greater pathology. **Accumulating evidence suggests that "low dose" IH (modest hypoxia, few episodes) may be a simple, safe, and effective treatment with considerable therapeutic potential for multiple clinical disorders**."

Veröffentlichung 36:

Hypoxic Conditioning as a New Therapeutic Modality (nih.gov)

In: Frontiers in Pediatrics. 2015; 3: 58.Published online 2015 Jun 22.
doi: 10.3389/fped.2015.00058

„Abstract

Preconditioning refers to a procedure by which a single noxious stimulus below the threshold of damage is applied to the tissue in order to increase resistance to the same or even different noxious stimuli given above the threshold of damage. Hypoxic preconditioning relies on complex and active defenses that organisms have developed to counter the adverse consequences of oxygen deprivation. The protection it confers against ischemic attack for instance as well as the underlying biological mechanisms have been extensively investigated in animal models. **Based on these data, hypoxic conditioning (consisting in recurrent exposure to hypoxia) has been suggested a potential non-pharmacological therapeutic intervention to enhance some physiological functions in individuals in whom acute or chronic pathological events are anticipated or existing. In addition to healthy subjects, some benefits have been reported in patients with cardiovascular and pulmonary diseases as well as in overweight and obese individuals.** Hypoxic conditioning consisting in sessions of intermittent exposure to moderate hypoxia repeated over several weeks may induce hematological, vascular, metabolic, and neurological effects. This review addresses the existing evidence regarding the use of hypoxic conditioning as a potential therapeutic modality, and emphasizes on many remaining issues to clarify and future researches to be performed in the field."

Veröffentlichung 37:

Exposure to mild intermittent hypoxia increases loop gain and the arousal threshold in participants with obstructive sleep apnoea - PubMed (nih.gov)

In: The Journal of Physiology. 2019 Jul;597(14):3697-3711.
doi: 10.1113/JP277711. Epub 2019 May 9.

„Abstract

Key points: Repeated daily mild intermittent hypoxia has been endorsed as a therapy to promote the recovery of respiratory and limb motor dysfunction. One possible side-effect of this therapy is an increase in apnoeic event number and duration, which is particularly relevant to participants with motor disorders coupled with an increased incidence of sleep apnoea. In this study, we report that increases in apnoeic event number and duration, following exposure to daily intermittent hypoxia, are the result of an increase in respiratory loop gain and the arousal threshold, in participants with

obstructive sleep apnoea. Daily exposure to mild intermittent hypoxia also led to an increase in the ventilatory response to arousal. Accordingly, individuals with motor disorders receiving mild intermittent hypoxia as a therapy should be screened for the presence of sleep apnoea, and if present, administration of intermittent hypoxia during hours of wakefulness should be combined with continuous positive airway pressure treatment during sleep.

Abstract: We determined if exposure to mild intermittent hypoxia (MIH) causes an increase in loop gain (LG) and the arousal threshold (AT) during non-rapid eye movement (NREM) sleep. Male participants with obstructive sleep apnoea (apnoea-hypopnoea index > 5 events/h), matched for age, body mass index and race were divided into two groups (n = 13 in each group). Following a baseline sleep study, one group was exposed to twelve 4-min episodes of hypoxia each day for 10 days and the other group to a sham protocol (SP). On Days 1 and 10, a sleep study was completed following exposure to MIH or the SP. For each sleep study, LG and the AT were measured during NREM sleep, using a model-based approach, and expressed as a fraction of baseline measures. LG increased after exposure to MIH (Day 1: 1.11 ± 0.03, P = 0.002, Day 10: 1.17 ± 0.05, P = 0.001), but not after the SP (Day 1: 1.03 ± 0.04, P = 1.0, Day 10: 1.0 ± 0.02, P = 1.0). AT also increased after exposure to MIH (Day 1: 1.13 ± 0.05, P = 0.01, Day 10: 1.19 ± 0.08, P = 0.05) but not after the SP (Day 1: 1.04 ± 0.05, P = 0.6, Day 10: 0.96 ± 0.04, P = 1.0). Our results might account for increases in apnoea frequency and duration previously observed during NREM sleep following exposure to MIH. **Our results also have implications for the use of MIH as a therapeutic modality.**"

Veröffentlichung 38:

Hypoxic training improves blood pressure, nitric oxide and hypoxia-inducible factor-1 alpha in hypertensive patients - PubMed (nih.gov)

In: European Journal of Applied Physiology. 2020 Aug;120(8):1815-1826.
doi: 10.1007/s00421-020-04410-9. Epub 2020 Jun 10.

„Abstract

Purpose: To examine the effects of intermittent hypoxic breathing at rest (IHR) or during exercise (IHT) on blood pressure and nitric oxide metabolites (NOx) and hypoxia-inducible factor-1 alpha levels (HIF-1α) over a 6-week period.

Methods: 47 hypertensive patients were randomly allocated to three groups: hypertensive control (CON: n = 17; IHR: n = 15 and IHT: n = 15. The CON received no intervention; whereas, IH groups received eight events of hypoxia (FIO2 0.14), and normoxia (FIO2 0.21), 24-min hypoxia and 24-min normoxia, for 6 weeks. The baseline data were collected 2 days before the intervention; while, the post-test data were collected at days 2 and 28 after the 6-week intervention.

Results: We observed a significant decrease of the SBP in both IH groups: IHR (- 12.0 ± 8.0 mmHg, p = 0.004 and - 9.9 ± 8.8 mmHg, p = 0.028, mean ± 95% CI) and IHT (- 13.0 ± 7.8 mmHg, p = 0.002 and - 10.0 ± 8.4 mmHg, p = 0.016) at days 2 and 28 post-intervention, respectively. Compared to CON, IHR and IHT had increased of NOx (IHR; 8.5 ± 7.6 µmol/L, p = 0.031 and IHT; 20.0 ± 9.1 µmol/L, p < 0.001) and HIF-1α (IHR; 170.0 ± 100.0 pg/mL, p = 0.002 and IHT; 340.5 ± 160.0 pg/mL, p < 0.001). At 2 days post-intervention, NOx and HIF-1α were negatively correlated with SBP in IHT.

**Conclusion: IH programs may act as an alternative therapeutic strategy for hypertension patients probably through elevation of NOx and HIF-1α production.“**

Veröffentlichung 38:

Intermittent Hypoxia Training for Treating Mild Cognitive Impairment: A Pilot Study - PubMed (nih.gov)

In: American Journals in Alzheimers Disease and other Dementias. Jan-Dec 2020;35:1533317519896725.
doi: 10.1177/1533317519896725

„Abstract

Although intermittent hypoxia training (IHT) has proven effective against various clinical disorders, its impact on mild cognitive impairment (MCI) is unknown. This pilot study examined IHT's safety and therapeutic efficacy in elderly patients with amnestic MCI (aMCI). Seven patients with aMCI (age 69 ± 3 years) alternately breathed 10% O2 and room-air, each 5 minutes, for 8 cycles/session, 3 sessions/wk for 8 weeks. The patients' resting arterial pressures fell by 5 to 7 mm Hg ($P < .05$) and cerebral tissue oxygenation increased ($P < .05$) following IHT. Intermittent hypoxia training enhanced hypoxemia-induced cerebral vasodilation ($P < .05$) and improved mini-mental state examination and digit span scores from 25.7 ± 0.4 to 27.7 ± 0.6 ($P = .038$) and from 24.7 ± 1.2 to 26.1 ± 1.3 ($P = .047$), respectively. California verbal learning test score tended to increase ($P = .102$), but trail making test-B and controlled oral word association test scores were unchanged. **Adaptation to moderate IHT may enhance cerebral oxygenation and hypoxia-induced cerebrovasodilation while improving short-term memory and attention in elderly patients with aMCI.**“

Veröffentlichung 39:

Intermittent hypoxia training: Powerful, non-invasive cerebroprotection against ethanol withdrawal excitotoxicity - PubMed (nih.gov)

In: Respiratory Physiology and Neurobiology. 2018 Oct;256:67-78.
doi: 10.1016/j.resp.2017.08.007. Epub 2017 Aug 12.

„Abstract

Ethanol intoxication and withdrawal exact a devastating toll on the central nervous system. Abrupt ethanol withdrawal provokes massive release of the excitatory neurotransmitter glutamate, which over-activates its postsynaptic receptors, causing intense Ca2+ loading, p38 mitogen activated protein kinase activation and oxidative stress, culminating in ATP depletion, mitochondrial injury, amyloid β deposition and neuronal death. Collectively, these mechanisms produce neurocognitive and sensorimotor dysfunction that discourages continued abstinence. Although the brain is heavily dependent on blood-borne O2 to sustain its aerobic ATP production, brief, cyclic episodes of moderate hypoxia and reoxygenation, when judiciously applied over the course of days or weeks, evoke adaptations that protect the brain from ethanol withdrawal-induced glutamate excitotoxicity, mitochondrial damage, oxidative stress and amyloid β accumulation. **This review summarizes evidence from ongoing preclinical research that demonstrates intermittent hypoxia training to be a**

**potentially powerful yet non-invasive intervention capable of affording robust, sustained neuroprotection during ethanol withdrawal.**“

Veröffentlichung 40:

Intermittent hypoxia training protects cerebrovascular function in Alzheimer's disease (nih.gov)

In: Experimental Biology and Medicine. 2016 Jun; 241(12): 1351–1363.Published online 2016 May 10.
doi: 10.1177/1535370216649060

„Abstract

Alzheimer's disease (AD) is a leading cause of death and disability among older adults. Modifiable vascular risk factors for AD (VRF) include obesity, hypertension, type 2 diabetes mellitus, sleep apnea, and metabolic syndrome. Here, interactions between cerebrovascular function and development of AD are reviewed, as are interventions to improve cerebral blood flow and reduce VRF. Atherosclerosis and small vessel cerebral disease impair metabolic regulation of cerebral blood flow and, along with microvascular rarefaction and altered trans-capillary exchange, create conditions favoring AD development. Although currently there are no definitive therapies for treatment or prevention of AD, reduction of VRFs lowers the risk for cognitive decline. **There is increasing evidence that brief repeated exposures to moderate hypoxia, i.e. intermittent hypoxic training (IHT), improve cerebral vascular function and reduce VRFs including systemic hypertension, cardiac arrhythmias, and mental stress. In experimental AD, IHT nearly prevented endothelial dysfunction of both cerebral and extra-cerebral blood vessels, rarefaction of the brain vascular network, and the loss of neurons in the brain cortex. Associated with these vasoprotective effects, IHT improved memory and lessened AD pathology. IHT increases endothelial production of nitric oxide (NO), thereby increasing regional cerebral blood flow and augmenting the vaso- and neuroprotective effects of endothelial NO. On the other hand, in AD excessive production of NO in microglia, astrocytes, and cortical neurons generates neurotoxic peroxynitrite. IHT enhances storage of excessive NO in the form of S-nitrosothiols and dinitrosyl iron complexes. Oxidative stress plays a pivotal role in the pathogenesis of AD, and IHT reduces oxidative stress in a number of experimental pathologies.** Beneficial effects of IHT in experimental neuropathologies other than AD, including dyscirculatory encephalopathy, ischemic stroke injury, audiogenic epilepsy, spinal cord injury, and alcohol withdrawal stress have also been reported. Further research on the potential benefits of IHT in AD and other brain pathologies is warranted.“

Veröffentlichung 41:

Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease - PubMed (nih.gov)

In: International Journal of Cardiology. 2004 Aug;96(2):247-54.
doi: 10.1016/j.ijcard.2003.07.021.

„Abstract

Background: Intermittent hypoxia has been suggested to increase exercise tolerance by enhancing stress resistance and improving oxygen delivery. Because the improvement of exercise tolerance reduces mortality in the elderly with and without coronary artery disease intermittent hypoxia might be a valuable preventive and therapeutic tool. However, controlled studies are lacking.

Methods and results: Sixteen males (50-70 years, 8 with and 8 without prior myocardial infarction) were randomly assigned in a double-blind fashion to receive 15 sessions of passive intermittent hypoxia (hypoxia group) or normoxia (control group) within 3 weeks. For the hypoxia group each session consisted of three to five hypoxic (14-10% oxygen) periods (3-5 min) with 3-min normoxic intervals. Controls inhaled only normoxic air in the same way. Exercise tests were performed before and after the 3-week breathing program. After 3 weeks of intermittent hypoxia peak oxygen consumption had increased compared to normoxic conditions (+ 6.2% vs.-3%, $p < 0.001$). This improvement was closely related to the enhanced arterial oxygen content after hypoxia ($r = 0.9$, $p < 0.001$). Both higher haemoglobin concentration and less arterial oxygen desaturation during exercise contributed to the increase in arterial oxygen content. During sub-maximal exercise (cycling at 1 W/kg) heart rate, systolic blood pressure, blood lactate concentration, and the rating of perceived exertion were diminished after intermittent hypoxia compared to control conditions (all $p < 0.05$). Changes in responses to exercise after intermittent hypoxia were similar in subjects with and without prior myocardial infarction.

**Conclusions: Three weeks of passive short-term intermittent hypoxic exposures increased aerobic capacity and exercise tolerance in elderly men with and without coronary artery disease**."

Veröffentlichung 42:

Intermittent Hypoxia–Hyperoxia Conditioning Improves Cardiorespiratory Fitness in Older Comorbid Cardiac Outpatients Without Hematological Changes: A Randomized Controlled Trial | Request PDF (researchgate.net)

In: High Altitude Medicine & Biology 19(4), September 2018
DOI: 10.1089/ham.2018.0014

„Abstract

Dudnik, Elena, Zagaynaya E, Glazachev OS, and Susta D. Intermittent Hypoxia-Hyperoxia Conditioning Improves Cardiorespiratory Fitness in Older Comorbid Cardiac Outpatients Without Hematological Changes: A Randomized Controlled Trial. High Alt Med Biol 00:000-000, 2018. Aim: To compare a program based on intermittent hypoxia-hyperoxia training (IHHT) consisting of breathing hypoxic-hyperoxic gas mixtures while resting to a standard exercise-based rehabilitation program with respect to cardiorespiratory fitness (CRF) in older, comorbid cardiac outpatients. Materials and methods: Thirty-two cardiac patients with comorbidities were randomly allocated to IHHT and control (CTRL) groups. IHHT completed a 5-week program of exposure to hypoxia-hyperoxia while resting, CTRL completed an 8-week tailored exercise program, and participants in the CTRL were also exposed to sham hypoxia exposure. CRF and relevant hematological biomarkers were measured at baseline and after treatment in both groups. Results: After intervention, CRF in the IHHT group was not significantly different (n = 15, 19.9 ± 6.1 mlO2 minutes-1 kg-1) compared with the CTRL group (n = 14, 20.6 ± 4.9 mlO2 minutes-1 kg-1). CRF in IHHT increased significantly from baseline (6.05 ± 1.6 mlO2 minutes-1 kg-1), while no difference was found in CTRL. Systolic and diastolic blood pressures

were not significantly different between groups after treatment. Hemoglobin content was not significantly different between groups. Erythrocytes and reticulocytes did not change pre/post interventions in both experimental groups. **Conclusions: IHHT is safe in patients with cardiac conditions and common comorbidities and it might be a suitable option for older patients who cannot exercise. A 5-week IHHT is as effective as an 8-week exercise program in improving CRF, without hematological changes.** Further studies are needed to clarify the nonhematological adaptations to short, repeated exposure to normobaric hypoxia-hyperoxia."

Veröffentlichung 43:

Interval hypoxic training in complex treatment of Helicobacter pylori-associated peptic ulcer disease - PubMed (nih.gov)

In: Acta Biochimica Polonica 2010;57(2):199-208. Epub 2010 Jun 8.

„Abstract

This study was aimed to demonstrate the efficacy of interval hypoxic training (IHT) in complex treatment of Helicobacter pylori-associated duodenal peptic ulcer disease (DPUD) by parameters of aerobic metabolism and indexes of heart rate variability (HRV). Eighty patients with H. pylori-associated DPUD were included into the study, mean age 32+/-1.8 yrs, duration of the disease up to 10 years (66.3 %). IHT was modulated using Frolov's hypoxicator (TDI-01) for 30 days after standard eradication therapy. Daily hypoxic sessions consisted of three one-minute sessions, one two-minute, and one three-minute sessions separated by one-minute intervals of room-air breathing. Use of IHT resulted in more efficient elimination of clinical symptoms, histological hallmarks of inflammation and signs of oxidative stress in glandulocytes of the gastric mucosa as determined by 4-hydroxynonenal accumulation. Moderate prooxidant activity of IHT was demonstrated by the increased level of TBARS and oxidatively modified products, normalization of hydroperoxides, middle mass molecules and atherogenic beta-lipoproteins with simultaneous increase in catalase activity and mild decline of SOD activity. Therefore, IHT appeared to be accompanied by higher intensity of redox reactions and enhanced regeneratory processes in cells and tissues. Significant increase in HRV was also noted. Such changes were associated with reduction of inflammation signs and modulation of the autonomic homeostasis in DPUD patients. **In general, use of IHT in complex treatment of H. pylori in DPUD patients can be recommended to increase resistance to oxidative stress and to modulate autonomic balance and oxidative homeostasis.**"

Veröffentlichung 44:

Cardioprotection by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential - PubMed (nih.gov)

In: American Journal of Physiology and Heart Circulation Physiology. 2018 Aug 1;315(2):H216-H232. doi: 10.1152/ajpheart.00060.2018. Epub 2018 Apr 13.

„Abstract

The calibrated application of limited-duration, cyclic, moderately intense hypoxia-reoxygenation increases cardiac resistance to ischemia-reperfusion stress. These intermittent hypoxic conditioning (IHC) programs consistently produce striking reductions in myocardial infarction and ventricular tachyarrhythmias after coronary artery occlusion and reperfusion and, in many cases, improve contractile function and coronary blood flow. These IHC protocols are fundamentally different from those used to simulate sleep apnea, a recognized cardiovascular risk factor. In clinical studies, IHC improved exercise capacity and decreased arrhythmias in patients with coronary artery or pulmonary disease and produced robust, persistent, antihypertensive effects in patients with essential hypertension. The protection afforded by IHC develops gradually and depends on β-adrenergic, δ-opioidergic, and reactive oxygen-nitrogen signaling pathways that use protein kinases and adaptive transcription factors. **In summary, adaptation to intermittent hypoxia offers a practical, largely unrecognized means of protecting myocardium from impending ischemia. The myocardial and perhaps broader systemic protection provided by IHC clearly merits further evaluation as a discrete intervention and as a potential complement to conventional pharmaceutical and surgical interventions.**“

Veröffentlichung 45:

(PDF) Effects of intermittent hypoxia-hyperoxia on mobility and perceived health in geriatric patients performing a multimodal training intervention: a randomized controlled trial (researchgate.net)

In: BMC Geriatrics 19(1), June 2019
DOI: 10.1186/s12877-019-1184-1

„Abstract and Figures

Background: Additional benefits of passive exposures to intermittent hypoxia and hyperoxia on cognitive performance and functional exercise capacity have been demonstrated in geriatric patients who performed a multimodal training program. The main goal of the present study was to evaluate effects of adding intermittent hypoxic-hyperoxic training (IHHT) to a multimodal training intervention (MTI) on mobility and perceived health in old individuals at a Geriatric Day Hospital. Methods: Thirty-four patients between 64 and 92 years participated in the double blind, randomized and controlled clinical trial. The elderly patients attended in a 5-7 weeks lasting MTI (strength, endurance, balance, reaction, flexibility, coordination, and cognitive exercises) and performed IHHT (breathing 10-14% oxygen for 4-7 min followed by 2-4 min 30-40% oxygen) in the Hypoxic Group (HG) or placebo treatment with ambient air in the Normoxic Group (NG) in parallel. Before and after all treatments, mobility was assessed by the Tinetti Mobility Test (TMT), the Timed-Up-and-Go Test (TUG) and Barthel-Index, while perceived health was assessed by one part of the EQ-5D Test, the EQ visual analogue scale (EQ VAS). Results: After the MTI plus IHHT or normoxia sessions, results of the TMT, TUG, Barthel Index and EQ-VAS revealed no significant difference between HG and NG (+ 14.9% vs + 15.4%, p = 0.25; - 21% vs - 26.3%, p = 0.51; + 4.2% vs + 3.6%, p = 0.56; + 37.9% vs + 33.9%, p = 0.24;). **Conclusions: IHHT added to MTI did not elicit additional improvements in perceived health and mobility compared to MTI alone**.“

Veröffentlichung 46:

Intermittent Hypoxia/Hyperoxia Versus Intermittent Hypoxia/Normoxia: Comparative Study in Prediabetes | High Altitude Medicine & Biology (liebertpub.com)

In: High Altitude Medicine & Biology Vol. 20, No. 4, 26 Dec 2019
https://doi.org/10.1089/ham.2019.0053

„Abstract

Background: Intermittent hypoxia/normoxia training (IHT) is considered a possible means to alleviate chronic diseases such as diabetes. In the last decade, another method of intermittent hypoxia/hyperoxia training (IHHT) began to enter the clinical practice, when the periods of breathing with atmospheric air are replaced by breathing a hyperoxic mixture. The present study compared the impact of adaptation to IHHT versus IHT on some metabolic variables in prediabetic patients.

Methods: A placebo-controlled trial included 55 patients with prediabetes, sea level residents, ages 51–74 years. Control Group (16 patients) took sham 3-week course, and the IHHT Group (17 patients) and IHT Group (22 patients) received similar actual sessions of IHHT or IHT five times a week for 3 weeks, each session consisting four cycles of 5 minutes of hypoxia (12% O2) followed by 3 minutes of hyperoxia (IHHT, 33% O2) or 5 minutes of normoxia (IHT, breathing room air). Fasting glucose, oral glucose tolerance test (OGTT), blood lipids, and the level of blood oxygen saturation (SpO2) were investigated at baseline, as well as 1 day and 1 month after IHHT/IHT termination.

Results: The study showed the same positive effect of two types of training: equal reduction of serum glucose concentrations, both fasting and 2 hours of OGTT; decreased total blood cholesterol and low-density lipoproteins; and an equally smaller drop in SpO2 during acute hypoxic test (breathing with 12% O2 for 20 minutes). Improved parameters persisted 1 month after training termination in both groups.

**Conclusion: One of the advantages of IHHT over IHT observed in this study could be some reduction in the duration of the sessions due to shortening reoxygenation periods. Further studies are required to search for additional beneficial effects of IHHT when using other training modes or other pathologies.“**

Veröffentlichung 47:

(PDF) Intermittent Hypoxia-Hyperoxia exposures Improve Cardiometabolic Profile, Exercise Tolerance and Quality of Life: A Preliminary Study in Cardiac Patients (researchgate.net)

In: Indian Journal of Public Health Research and Development 9(1):208, January 2018
DOI: 10.5958/0976-5506.2018.00039.6

„Abstract

Study design: randomized controlled before-and-after and in follow-up trial. Forty-six CAD patients volunteered to take part in the study: a group of 27 patients undertook an Intermittent Hypoxia (O2 at 10%) - Hyperoxia (O2 at 30%) Training (IHHT), while a control group (CTRL) of 19 patients was allocated to sham IHHT treatment (breathing via face mask by room air, O2 at 21%). Exercise performance, blood and metabolic profile, quality of life (MOS SF-36, Seattle Angina Questionnaire, SAQ) were measured before and after IHHT/sham IHHT in both groups; the intervention group was also assessed one month after completing the IHHT. The IHHT intervention group showed improved

exercise capacity (+1,8 ml O2/min/kg, p=0,02), reduced resting systolic and diastolic blood pressures (151/85 before vs 130/73 after p<0,01), enhanced Left Ventricle Ejection Fraction (62,6±5,5% vs 58±6,2%, p<0,01), glycemia was significantly reduced only at 1-month follow-up (6,18±1,7 after vs 7,10±2,34 mmol/l at baseline, p=0,037). Frequency of angina as reason to stop exercising was significantly reduced after treatment and at 1-month follow-up. **In CAD patients an Intermittent Hypoxia-Hyperoxia Training program is associated with improved exercise tolerance, risks factors profile and quality of life (SF-36, SAQ). IHHT has proved to be safe, well tolerable and easily applicable in cardiac patients.**"

Veröffentlichung 48:

ADAPTATION TO INTERVAL HYPOXIAHYPEROXIA IMPROVES EXERCISE TOLERANCE IN PROFESSIONAL ATHLETES: EXPERIMENTAL SUBSTANTIATION AND APPLIED APPROBATION | European Scientific Journal, ESJ (eujournal.org)

In: European Scientific Journal June 2014 edition vol.10, No.18 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431

„Abstract

A theoretical substantiation and experimental testing of combined adaptation to changing oxygen levels in the enhancement of tolerance to physical loads and pilot study on the protective effects of a novel strategy for adaptation to interval hypoxia-hyperoxia aimed at eliminating the overtraining syndrome in professional athletes, have been carried out. Methods On the experimental step, adaptation of male Wistar rats was performed in 2 modes: 1) hypoxia-normoxia (H/N): 2) a new model - hypoxia-hyperoxia (H/H), 1h daily for 15 days. Acute physical load (APL) consisted in swimming (21oC) to exhaustion. Intensity of free radical oxidation was estimated by the rate of accumulation of lipid peroxidation products in the course of induction in the Fe2++ ascorbate system in vitro. Activities of antioxidant enzymes were measured by spectrophotometria, levels of inducible HSP72, HSP32 and constituitive HSC73 were measured by Western blot analysis with monoclonal antibodies. On the pilot study 15 male and female middle-distance runners with overtraining syndrome wereexposed to interval hypoxia-hyperoxia training (IHHT) sessions. Working capacity (PWC170), hypoxic tolerance, haematological parameters and heart rate variability (HRV) analysis were determined before and 3 days after IHHT sessions. Results In experiments combination of adaptation to physical exercise with adaptation to hypoxia-hyperoxia improves tolerance under conditions of APL: short-term adaptation to physical exercise compensates for stress, but not for the hypoxic component of APL, while physical training combined with adaptation to hypoxia-hyperoxia fully compensates for both components. In 15 young professional athletes with overtraining syndrome combination of IHHT with low-intensity exercise restores the autonomic balance and physical capacity (significant elevation of PWC170 index, maximal oxygen consumption VO2max, and VO2max/kg). **Conclusion Adaptation to interval hypoxia-hyperoxia provides optimization of the hypoxic and stress componentsinexercise tolerance systemic response which is revealed in experimental studies and supported by the data of young athletes with overtraining syndrome rehabilitation.**"

Veröffentlichung 49:

Hypoxia and Hyperoxia Affect Serum Angiogenic Regulators in T2DM Men during Cycling - PubMed (nih.gov)

In: International Journal of Sports Medicine. 2017 Feb;38(2):92-98.
doi: 10.1055/s-0042-116823. Epub 2017 Jan 9.

„Abstract

Exercise-induced transient increases in pro-angiogenic regulators can promote angiogenesis.This pilot study aims to analyze the potential of exercise to positively affect angiogenic regulators in patients with type 2 diabetes mellitus (T2DM), who often exhibit abnormal angiogenesis, under different environmental conditions. 9 overweight/obese men with uncomplicated T2DM (8 took anti-diabetic drugs) performed submaximal cycling for 40 min in normoxia (≈21 vol%O2), hypoxia (≈14 vol %O2) and during alternating hypoxia/hyperoxia (≈14 vol%O2/≈30 vol%O2, 5-min intervals) (3×3 crossover design). Serum pro-angiogenic vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-2, MMP-9 and anti-angiogenic endostatin were quantified using enzyme-linked immunosorbent assay (ELISA) kits. Non-parametric statistical tests (Wilcoxon, Friedman analysis of variance) were applied. VEGF increased significantly from pre- to post-exercise with hypoxia and hypoxia/hyperoxia. MMP-2 increased significantly in all experimental runs, while MMP-9 only increased significantly with hypoxia and hypoxia/hyperoxia. Endostatin increased significantly with normoxia and hypoxia. However, the magnitude of changes did not differ significantly between conditions. Capillary blood lactate was significantly lower following cycling with hypoxia/hyperoxia than with hypoxia alone. Although differences in subjective ratings of perceived exertion failed significance, 7 subjects were less exerted with hypoxia/hyperoxia than with hypoxia. **Submaximal cycling with hypoxia or alternating hypoxia/hyperoxia may induce a more reliable up-regulation of pro-angiogenic regulators compared with normoxia, while hypoxia/hyperoxia may be better tolerated than hypoxia alone.**“

Veröffentlichung 50:

Intermittent hypoxia conditioning prevents endothelial dysfunction and improves nitric oxide storage in spontaneously hypertensive rats - PubMed (nih.gov)

In: Experimental Biology and Medicine (Maywood). 2011 Jul;236(7):867-73.
doi: 10.1258/ebm.2011.011023. Epub 2011 Jun 7.

„Abstract

Although intermittent hypoxia is often associated with hypertension, experimental and clinical studies have demonstrated definite antihypertensive effects of some intermittent hypoxia conditioning (IHC) regimens. Mechanisms of this antihypertensive response are unknown. Endothelial dysfunction related to disturbed synthesis and/or reduced availability of nitric oxide (NO) has been linked to hypertension. Thus, experiments were conducted to determine if IHC can improve endothelium-dependent relaxation and formation of releasable vascular NO stores of young (4-8-week-old) spontaneously hypertensive rats (SHR). Rats were subjected to either IHC (9.5-10% O(2), 5-10 min, 5-8 times per day, 20 d) or to sham conditioning. Endothelium-dependent relaxation to acetylcholine was measured in norepinephrine-precontracted, isolated aortic rings, and the size of NO stores was evaluated by percent relaxation to N-acetylcysteine (NAC), which releases stored NO. The capacity of aortic rings for NO storage was evaluated by the relaxation to NAC after prior

incubation with an NO donor. IHC significantly suppressed the development of hypertension in young SHR. Endothelial function decreased from 54.7 ± 4.6% to 28.1 ± 6.4% relaxation to acetylcholine after 20 d of sham IHC, whereas endothelial function was sustained (60.3 ± 6.0% relaxation) in IHC rats. IHC also induced formation of available NO stores and enhanced the capacity of aortic rings to store NO. **Therefore, the antihypertensive effect of IHC in young SHR is associated with prevention of endothelial dysfunction and with increased accumulation of NO stores in vascular walls**."

Veröffentlichung 51:

Effects of intermittent hypoxia training on exercise performance, hemodynamics, and ventilation in healthy senior men - PubMed (nih.gov)

In: High Altitude Medicine & Biology. Spring 2008;9(1):43-52.
doi: 10.1089/ham.2007.1053.

„Abstract

The efficacy and safety of intermittent hypoxia training (IHT) were investigated in healthy, 60- to 74-yr-old men. Fourteen men (Gr 1) who routinely exercised daily for 20 to 30 min were compared with 21 (Gr 2) who avoided exercise. Their submaximal work-load power values before the IHT training were 94 +/- 3.7 and 66 +/- 3.1, respectively. Before and after 10 days of IHT, the ventilatory response to sustained hypoxia (SH; 12% O(2) for 10 min), work capacity (bicycle ergometer), and forearm cutaneous perfusion (laser Doppler) were determined. During SH, no negative electrocardiogram (ECG) changes were observed in either group, and the ventilatory response to SH was unaltered by IHT. In Gr 1, IHT (normobaric rebreathing for 5 min, final Sa(O(2)) = 85% to 86%, followed by 5 min normoxia, 4/day) produced no changes in hemodynamic indixes and work capacity. In Gr 2, IHT decreased blood pressure (BP) by 7.9 +/- 3.1 mmHg ($p < 0.05$) and increased submaximal work by 11.3% ($p < 0.05$) and anaerobic threshold by 12.7% ($p < 0.05$). The increase in HR and BP caused by a 55 W-work load was reduced by 5% and 6.5%, respectively ($p < 0.05$). Cutaneous perfusion increased by 0.06 +/- 0.04 mL/min/100 g in Gr 1 and by 0.11 +/- 0.04 mL/min/100 g in Gr 2 ($p < 0.05$). Hyperemia recovery time increased significantly by 15.3 +/- 4.6 sec in Gr 1 and by 25.2 +/- 11.2 sec in Gr 2**. Thus, healthy senior men well tolerate IHT as performed in this investigation. In untrained, healthy senior men, IHT had greater positive effects on hemodynamics, microvascular endothelial function, and work capacity**."

Veröffentlichung 52:

Effects of intermittent hypoxia training on exercise performance, hemodynamics, and ventilation in healthy senior men - PubMed (nih.gov)

In: High Altitude Medicine & Biology. Spring 2008;9(1):43-52.
doi: 10.1089/ham.2007.1053.

„Abstract

The efficacy and safety of intermittent hypoxia training (IHT) were investigated in healthy, 60- to 74-yr-old men. Fourteen men (Gr 1) who routinely exercised daily for 20 to 30 min were compared with 21 (Gr 2) who avoided exercise. Their submaximal work-load power values before the IHT training were 94 +/- 3.7 and 66 +/- 3.1, respectively. Before and after 10 days of IHT, the ventilatory response

to sustained hypoxia (SH; 12% O(2) for 10 min), work capacity (bicycle ergometer), and forearm cutaneous perfusion (laser Doppler) were determined. During SH, no negative electrocardiogram (ECG) changes were observed in either group, and the ventilatory response to SH was unaltered by IHT. In Gr 1, IHT (normobaric rebreathing for 5 min, final Sa(O(2)) = 85% to 86%, followed by 5 min normoxia, 4/day) produced no changes in hemodynamic indixes and work capacity. In Gr 2, IHT decreased blood pressure (BP) by 7.9 +/- 3.1 mmHg ($p < 0.05$) and increased submaximal work by 11.3% ($p < 0.05$) and anaerobic threshold by 12.7% ($p < 0.05$). The increase in HR and BP caused by a 55 W-work load was reduced by 5% and 6.5%, respectively ($p < 0.05$). Cutaneous perfusion increased by 0.06 +/- 0.04 mL/min/100 g in Gr 1 and by 0.11 +/- 0.04 mL/min/100 g in Gr 2 ($p < 0.05$). Hyperemia recovery time increased significantly by 15.3 +/- 4.6 sec in Gr 1 and by 25.2 +/- 11.2 sec in Gr 2**. Thus, healthy senior men well tolerate IHT as performed in this investigation. In untrained, healthy senior men, IHT had greater positive effects on hemodynamics, microvascular endothelial function, and work capacity**."

Veröffentlichung 53:

Intermittent hypoxia training as non-pharmacologic therapy for cardiovascular diseases: Practical analysis on methods and equipment (nih.gov)

In: Experimental Biology and Medicine (Maywood). 2016 Sep; 241(15): 1708–1723.Published online 2016 Jul 12.
doi: 10.1177/1535370216657614

„Abstract

The global industrialization has brought profound lifestyle changes and environmental pollutions leading to higher risks of cardiovascular diseases. Such tremendous challenges outweigh the benefits of major advances in pharmacotherapies (such as statins, antihypertensive, antithrombotic drugs) and exacerbate the public healthcare burdens. One of the promising complementary non-pharmacologic therapies is the so-called intermittent hypoxia training (IHT) via activation of the human body's own natural defense through adaptation to intermittent hypoxia. This review article primarily focuses on the practical questions concerning the utilization of IHT as a non-pharmacologic therapy against cardiovascular diseases in humans. Evidence accumulated in the past five decades of research in healthy men and patients has suggested that short-term daily sessions consisting 3–4 bouts of 5–7 min exposures to 12–10% O2 alternating with normoxic durations for 2–3 weeks can result in remarkable beneficial effects in treatment of cardiovascular diseases such as hypertension, coronary heart disease, and heart failure. Special attentions are paid to the therapeutic effects of different IHT models, along with introduction of a variety of specialized facilities and equipment available for IHT, including hypobaric chambers, hypoxia gas mixture deliver equipment (rooms, tents, face masks), and portable rebreathing devices. Further clinical trials and thorough evaluations of the risks versus benefits of IHT are much needed to develop a series of standardized and practical guidelines for IHT. **Taken together, we can envisage a bright future for IHT to play a more significant role in the preventive and complementary medicine against cardiovascular diseases**."

Veröffentlichung 54:

High-Intensity Interval Training in Normobaric Hypoxia Leads to Greater Body Fat Loss in Overweight/Obese Women than High-Intensity Interval Training in Normoxia - PubMed (nih.gov)

In: Frontiers in Physiology. 2018 Feb 7;9:60.
doi: 10.3389/fphys.2018.00060. eCollection 2018.

„Abstract

A moderate hypoxic stimulus is considered a promising therapeutic modality for several pathological states including obesity. There is scientific evidence suggesting that when hypoxia and physical activity are combined, they could provide benefits for the obese population. The aim of the present study was to investigate if exposure to hypoxia combined with two different protocols of high-intensity interval exercise in overweight/obese women was more effective compared with exercise in normoxia. Study participants included 82 overweight/obese women, who started a 12 week program of 36 sessions, and were randomly divided into four groups: (1) aerobic interval training in hypoxia (AitH; FiO2 = 17.2%; n = 13), (2) aerobic interval training in normoxia (AitN; n = 15), (3) sprint interval training in hypoxia (SitH; n = 15), and (4) sprint interval training in normoxia (SitN; n = 18). Body mass, body mass index, percentage of total fat mass, muscle mass, basal metabolic rate, fat, and carbohydrate oxidation, and fat and carbohydrate energy were assessed. Outcomes were measured at baseline (T1), after 18 training sessions (T2), 7 days after the last session (T3), and 4 weeks after the last session (T4). The fat mass in the SitH group was significantly reduced compared with the SitN group from T1 to T3 ($p < 0.05$) and from T1 to T4 ($p < 0.05$) and muscle mass increased significantly from T1 to T4 ($p < 0.05$). Fat mass in the AitH group decreased significantly ($p < 0.01$) and muscle mass increased ($p = 0.022$) compared with the AitN group from T1 to T4. All training groups showed a reduction in the percentage of fat mass, with a statistically significant reduction in the hypoxia groups ($p < 0.05$). Muscle mass increased significantly in the hypoxia groups ($p < 0.05$), especially at T4. While fat oxidation tended to increase and oxidation of carbohydrates tended to decrease in both hypoxia groups, the tendency was reversed in the normoxia groups. **Thus, high-intensity interval training under normobaric intermittent hypoxia for 12 weeks in overweight/obese women seems to be promising for reducing body fat content with a concomitant increase in muscle mass**.“

Veröffentlichung 55:

The effect of short-term intermittent hypoxic exposure on heart rate variability in a sedentary population - PubMed (nih.gov)

In: Physiology International. 2016 Mar;103(1):75-85.
doi: 10.1556/036.103.2016.1.7.

„Abstract

While the effects of instantaneous, single-bout exposure to hypoxia have been well researched, little is known about the autonomic response during, or as an adaptation to, repeated intermittent hypoxic exposure (IHE) in a sedentary population. Resting heart rate variability (HRV) and exercise capacity was assessed in 16 participants (8 receiving IHE, [Hyp] and 8 receiving a placebo treatment [C]) before and after a 4-week IHE intervention. Heart rate variability was also measured during an IHE session in the last week of the intervention. Post-intervention, the root mean squared successive difference (rMSSD) increased substantially in Hyp (71.6 ± 52.5%, mean change ± 90% confidence limits) compared to C suggesting an increase in vagal outflow. However, aside from a likely decrease

in submaximal exercise heart rate in the Hyp group (-5.0 ± 6.4%) there was little evidence of improved exercise capacity. During the week 4 IHE measurement, HRV decreased during the hypoxic exposure (reduced R-R interval: -7.5 ± 3.2%; and rMSSD: -24.7 ± 17.3%) suggesting a decrease in the relative contribution of vagal activity. **In summary, while 4 weeks of IHE is unlikely to improve maximal exercise capacity, it may be a useful means of increasing HRV in people unable to exercise**."

Veröffentlichung 56:

Intermittent hypoxia training in prediabetes patients: Beneficial effects on glucose homeostasis, hypoxia tolerance and gene expression - PubMed (nih.gov)

In: Experimental Biology and Medicine (Maywood). 2017 Sep;242(15):1542-1552.
doi: 10.1177/1535370217723578. Epub 2017 Jul 31.

„Abstract

The present study aimed at examining beneficial effects of intermittent hypoxia training (IHT) under prediabetic conditions. We investigate the effects of three-week IHT on blood glucose level, tolerance to acute hypoxia, and leukocyte mRNA expression of hypoxia inducible factor 1α (HIF-1α) and its target genes, i.e. insulin receptor, facilitated glucose transporter-solute carrier family-2, and potassium voltage-gated channel subfamily J. Seven healthy and 11 prediabetic men and women (44-70 years of age) were examined before, next day and one month after three-week IHT (3 sessions per week, each session consisting 4 cycles of 5-min 12% O2 and 5-min room air breathing). We found that IHT afforded beneficial effects on glucose homeostasis in patients with prediabetes reducing fasting glucose and during standard oral glucose tolerance test. The most pronounced positive effects were observed at one month after IHT termination. IHT also significantly increased the tolerance to acute hypoxia (i.e. SaO2 level at 20th min of breathing with 12% O2) and improved functional parameters of respiratory and cardiovascular systems. IHT stimulated HIF-1α mRNA expression in blood leukocytes in healthy and prediabetic subjects, but in prediabetes patients the maximum increase was lagged. The greatest changes in mRNA expression of HIF-1α target genes occurred a month after IHT and coincided with the largest decrease in blood glucose levels. The higher expression of HIF-1α was positively associated with higher tolerance to hypoxia and better glucose homeostasis. In conclusion, our results suggest that IHT may be useful for preventing the development of type 2 diabetes. Impact statement The present study investigated the beneficial effects of intermittent hypoxia training (IHT) in humans under prediabetic conditions. **We found that three-week moderate IHT induced higher HIF-1α mRNA expressions as well as its target genes, which were positively correlated with higher tolerance to acute hypoxia and better glucose homeostasis in both middle-aged healthy and prediabetic subjects. This small clinical trial has provided new data suggesting a potential utility of IHT for management of prediabetes patients.**"

Veröffentlichung 57:

(PDF) Adaptation to Intermittent Hypoxia-Hyperoxia in the Rehabilitation of Patients With Ischemic Heart Disease: Exercise Tolerance and Quality of Life (researchgate.net)

In: Kardiologiia 57(5):10-16, May 2017
DOI: 10.18565/cardio.2017.5.10-16

„Abstract

Aim: to assess effect of interval hypoxic-hyperoxic training (IT) on exercise tolerance and quality of life of patients with ischemic heart disease (IHD) receiving optimal medical therapy, as well as the safety of IHHT use. Methods: Patients with stable IHD with functional class II and III angina (n=46) were randomized into two groups: IHHT (n=27, 15 treatments in 3 weeks), and IHHT imitation (n=19). Cardiopulmonary stress test was performed to evaluate the following parameters of exercise tolerance: peak oxygen consumption (VO2peak, VO2peak/kg), % of predicted peak oxygen consumption (%VO2 peak) and anaerobic threshold (VO2AT). MOS SF-36, SAQ, HADS questionnaires were used for assessment of quality of life (QL). Results: Exercise tolerance (VO2peak/kg) after course of IHHT significantly increased (p=0.03) and remained significantly elevated during subsequent month (p=0.036). **Marked improvement was also observed in patients subjective perception of QL**. **This was evidenced by dynamics of characteristics of physical functioning as well as of psychological state, significant increase of values on all scales of disease-specific questionnaire SAQ, reduction of depression and anxiety according to dynamics of HADS scores. These effects persisted in 1 month after IHHT. IHHT was safe and well tolerated.** Side effects were minimal (transient slight dizziness, feeling of shortage of air) and did not require IHHT termination. **Conclusion: We received clinical confirmation of safety and effectiveness in of IHHT in medically treated patients with stable angina. IHHT was associated with significant improvement of exercise tolerance, subjective perception of QL, reduction of number of angina attacks. Thus, IHHT has significant potential as component of complex treatment and rehabilitation of patients with stable angina.**“

Veröffentlichung 58:

(PDF) Intermittent Hypoxia-Hyperoxia exposures Improve Cardiometabolic Profile, Exercise Tolerance and Quality of Life: A Preliminary Study in Cardiac Patients (researchgate.net)

In: Indian Journal of Public Health Research and Development 9(1):208, January 2018
DOI: 10.5958/0976-5506.2018.00039.6

„Abstract

Study design: randomized controlled before-and-after and in follow-up trial. Forty-six CAD patients volunteered to take part in the study: a group of 27 patients undertook an Intermittent Hypoxia (O2 at 10%) - Hyperoxia (O2 at 30%) Training (IHHT), while a control group (CTRL) of 19 patients was allocated to sham IHHT treatment (breathing via face mask by room air, O2 at 21%). Exercise performance, blood and metabolic profile, quality of life (MOS SF-36, Seattle Angina Questionnaire, SAQ) were measured before and after IHHT/sham IHHT in both groups; the intervention group was also assessed one month after completing the IHHT. The IHHT intervention group showed improved exercise capacity (+1,8 ml O2/min/kg, p=0,02), reduced resting systolic and diastolic blood pressures (151/85 before vs 130/73 after p<0,01), enhanced Left Ventricle Ejection Fraction (62,6±5,5% vs 58±6,2%, p<0,01), glycemia was significantly reduced only at 1-month follow-up (6,18±1,7 after vs 7,10±2,34 mmol/l at baseline, p=0,037). Frequency of angina as reason to stop exercising was significantly reduced after treatment and at 1-month follow-up. **In CAD patients an Intermittent Hypoxia-Hyperoxia Training program is associated with improved exercise tolerance, risks factors profile and quality of life (SF-36, SAQ). IHHT has proved to be safe, well tolerable and easily applicable in cardiac patients.**“

Veröffentlichung 59:

Advancing hypoxic training in team sports: from intermittent hypoxic training to repeated sprint training in hypoxia - PubMed (nih.gov)

In: British Journal of Sports Medicine. 2013 Dec;47 Suppl 1(Suppl 1):i45-50.
doi: 10.1136/bjsports-2013-092741.

„Abstract

Over the past two decades, intermittent hypoxic training (IHT), that is, a method where athletes live at or near sea level but train under hypoxic conditions, has gained unprecedented popularity. By adding the stress of hypoxia during 'aerobic' or 'anaerobic' interval training, it is believed that IHT would potentiate greater performance improvements compared to similar training at sea level. A thorough analysis of studies including IHT, however, leads to strikingly poor benefits for sea-level performance improvement, compared to the same training method performed in normoxia. Despite the positive molecular adaptations observed after various IHT modalities, the characteristics of optimal training stimulus in hypoxia are still unclear and their functional translation in terms of whole-body performance enhancement is minimal. To overcome some of the inherent limitations of IHT (lower training stimulus due to hypoxia), recent studies have successfully investigated a new training method based on the repetition of short (<30 s) 'all-out' sprints with incomplete recoveries in hypoxia, the so-called repeated sprint training in hypoxia (RSH). The aims of the present review are therefore threefold: first, to summarise the main mechanisms for interval training and repeated sprint training in normoxia. Second, to critically analyse the results of the studies involving high-intensity exercises performed in hypoxia for sea-level performance enhancement by differentiating IHT and RSH. Third, to discuss the potential mechanisms underpinning the effectiveness of those methods, and their inherent limitations, along with the new research avenues surrounding this topic.“

Veröffentlichung 60:

Effects of a single bout of interval hypoxia on cardiorespiratory control and blood glucose in patients with type 2 diabetes - PubMed (nih.gov)

In: Diabetes Care. 2013 Aug;36(8):2183-9.
doi: 10.2337/dc12-2113. Epub 2013 Mar 27.

„Abstract

Objective: Hypoxia may cause functional autonomic imbalance in diabetes. Intermittent hypoxia (IH), a technique improving the adaptation to hypoxia, might improve cardiorespiratory reflexes and, ultimately, blood glucose concentrations in patients with type 2 diabetes. We tested whether a single bout of IH could initiate a long-lasting response potentially leading to better adaptation to hypoxia.

Research design and methods: In 14 patients with type 2 diabetes without autonomic complications, we measured blood pressure, heart rate, oxygen saturation, chemoreflex (hypoxic and hypercapnic ventilatory responses, ventilatory recruitment threshold), and baroreflex sensitivity before, immediately after, and 3 and 6 h after a 1-h single bout of IH (6-min breathing of 13% oxygen mixture 5 times each separated by 6-min recovery). The measurements were repeated on a placebo day (at

least 1 week apart, in random sequence) when subjects were only breathing room air (single-blind protocol).

Results: IH significantly increased hypercapnic ventilatory responses and reduced ventilatory recruitment threshold, and increased oxygen saturation and blood pressures, whereas increases in heart rate variability and baroreflex sensitivity were not significant. Blood glucose significantly decreased after IH. No such changes were observed during the placebo day, except an increase in oxygen saturation. Some of the effects lasted 3 h after IH, and some even persisted until 6 h after IH.

**Conclusions: A single bout of IH induced an initial adaptation to hypoxia, with improvement in cardiorespiratory reflexes and reduction in blood glucose. Patients with type 2 diabetes could potentially benefit from the application of a full (>2 weeks) IH intervention.**"

Veröffentlichung 61:

Effects training in hypoxia on cardiometabolic parameters in obese people: A systematic review of randomized controlled trial - PubMed (nih.gov)

In: Atencion Primaria. Aug-Sep 2019;51(7):397-405.
doi: 10.1016/j.aprim.2018.03.011. Epub 2018 Aug 29.

„Abstract …

Objective: The aim of the present review is to evaluate effects of intermittent hypoxia and exercise therapy in cardiometabolic parameters on adult obese people.

Database: Three well-known databases were selected: EMBASE, MEDLINE and Web of Science. Studies selection: Inclusion criteria were: (a) human healthy overweight or obese adults, (b) study randomized controlled trial, (c) original experimental study, (d) English languages and (e) therapy with intermittent hypoxia and exercise.

Design: The assessment of the methodological quality of each study was based upon the risk of bias (PEDro scale) and level of evidence (CBO Guidelines).

Data extraction: five articles clearly met inclusion criteria and were reviewed to data extraction.

Results: In the hypoxia groups, weight, body mass index, waist circumference, waist-hip ratio, fat mass and lean mass improved in at least two studies in comparison with the baseline. Systolic blood pressure improved in one study. The lipid profile and the aerobic capacity were not reduced significantly.

**Conclusions: Results suggest that combined hypoxia with exercise may help to improve cardiometabolic parameters in obese people.“**

Veröffentlichung 62:

(PDF) Post-metabolic response to passive normobaric hypoxic exposure in sedendary overweight males: A pilot study (researchgate.net)

In: Nutrition & Metabolism 9(1):103, November 2012
DOI: 10.1186/1743-7075-9-103

„Abstract …

Background The present pilot study was designed to test the impact of passive acute normobaric hypoxic exposure (PAH) and passive short-term normobaric hypoxic exposure (PSH) conditions on energy expenditure (EE) and substrates utilisation (glucose and lipid oxidation). Methods Eleven participants have completed the PAH session while the control group (CG) underwent a simulated experimental condition in normobaric normoxic condition. A subset of 6 participants underwent an additional six 3-hour sessions on consecutive days. Metabolic rates were obtained pre- and post-treatments on the morning following an overnight (12 hours) fast in PAH, PSH, and CG groups. Results The statistical outcomes showed a significant increase in EE for PAH, control, and PSH while a shift in substrate utilization towards lipid sources was only detected for PAH and PSH, respectively. Conclusion This pilot study showed that passive acute normobaric hypoxic exposure did affect EE and fuel utilization in sedentary overweight males and that further passive normobaric hypoxic exposures (PSH) magnified these metabolic adjustments. **These outcomes provide valuable information for further research in the area of hypoxia as a new therapeutic strategy to improve the management of weight loss.“**

Veröffentlichung 63:

Intermittent hypoxia exposure prevents mtDNA deletion and mitochondrial structure damage produced by ischemia/reperfusion injury - PubMed (nih.gov)

In: Sheng Li Xue Bao (Acta Physiologica sinica). 2000 Oct;52(5):375-80.

„Abstract

In the present study, polymerase chain reaction (PCR) was conducted to determine mtDNA(4834) deletion, and myocardial ultrastructure was visualized by electron microscope to see whether intermittent hypoxia (high altitude) adaptation exerts some action on mitochondria against ischemia/reperfusion injury. Myocardial ischemia/reperfusion in isolated perfused rat hearts induced severe damage to the ultrastructure of myocardial mitochondria and mtDNA4834 deletion down to 87.5% of normoxia rats. After the rats were exposed to intermittent hypoxia (5000 m; 6 h/d for 28 d), the myocardial structure was well reserved and mtDNA(4834) deletion dropped to 28.57%of control ($P<0.05$). **It is suggested that intermittent hypoxia adaptation prevents mtDNA deletion, and preserves normal structure of mitochondria, which would be beneficial to the maintenance of normal mitochondrial function, and increases tolerance of myocardium against ischemia/reperfusion injury.**“