REPORT

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Intermittent hypoxic training as an effective method of activation therapy

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Abstract

This article considers possibilities of achieving the most effective therapeutic effect of intermittent hypoxia training (IHT) by initiating an activation and training reaction. Thanks to IHT the body builds an anti-stress type adaptation which increases the body's nonspecific resistance to the development of diseases. It works through a variable functional load which includes a mechanism for optimizing mitochondrial respiration and is a trigger for synchronizing the performance of the nervous, immune and hormonal systems. Some biochemical data presented in the article demonstrate the effects of moderate hypoxia. In addition, laboratory and hardware methods of diagnosing for the selection of individual IHT regimes are proposed. IHT is used to great effect in training of astronauts, pilots, athletes and in the treatment of diabetes mellitus, trophic ulcers, diseases of the cardiovascular system, the central nervous system and oncological disorders as well as for rejuvenation purposes.

Keywords

Intermittent hypoxia training, Activation therapy, Adaptation, Stress, Sport performance, Aging diseasses, Lactic acid, Depression, Anorexia, Nitric oxide, Hypoxia inducible factor – 1 (HIF–1)

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Introduction

Activation therapy is the impact on the human body of various biologically active factors, including adaptogens, physiotherapy or other stimuli to obtain a general nonspecific reaction by the body that manifests itself in an increase in its viability. These effects have positive impacts, directly or indirectly, through an increase in the effectiveness of tissue respiration.

At the present time, much experimental material has been accumulated on the beneficial effects of natural and experimental hypoxia on the human body. A special contribution to the study was made by N.A. Agadzhanyan [1–5]; R.B. Strelkov and A.Ya. Chizhov [6–10]; N.I. Volkov [11], A.Z. Kolchinskaya [12–14]; S.G. Krivoshchekov [15, 16] and many others. In recent years, controlled Intermittent Hypoxic Training (IHT) is widely used in clinical medicine. IHT is a method of increasing nonspecific resistance of the body via adaptation to hypoxia which leads to the effectiveness of mitochondrial respiration.

Gas exchange is the fastest metabolism regulator. Oxygen we breathe is a natural stimulus, an activator that changes metabolism, expanding the range of adaptation. By changing the amount of oxygen in the gas composition, we directly affect mitochondrial respiration. A reduction in oxygen tension in arterial blood and tissues is acting as a reflex stimulus of receptive fields and nerve centers, which regulates physiological processes [17, 18]. In this case, the stimulus itself is habitual for the organism and, within certain limits, does not cause inadequate reactions [19,20]. That is why hypnotic training proved to be a successful tool for increasing the resistance of the

human body to factors in aviation and space flights [21-23], to achieve maximum sports results [1] and increase the overall resistance of the body to adverse effects.

Materials and methods

Under clinical conditions, hypoxic training with alternating breathing of ambient air is most often encountered with a mixture of 10–14 % oxygen (O_2) and about 86–90 % nitrogen (N_2) at normal atmospheric pressure (through a mask for 3-5 minutes), 6–9 cycles, with pauses between cycles of 3–5 minutes (respiration air at sea level, i.e. 20.9 % O_2). The duration of the session is 45–90 minutes. Adaptation develops as a result of breathing a hypoxic gas mixture, in a discontinuous mode, which leads to the repeated shift,"swing", of oxygen saturation in blood (SpO_2) from 100–94 % to 86–78 %. We are alternating tension and rest.The oxygen content in the inhaled air varies from 20.9 % (room air) to 10–14 % (through the mask). Rocking mode, "swing", is the main key to successful treatment and training.

Youth is the flexibility in providing compliance with external influences. Old age and degenerative diseases are the rigidity in physiology and psychology. From our point of view, due to the "swing regime" of oxygen tension in the arterial blood and tissues, which we estimate by oxygen saturation, adaptive reactions develop. Monitoring and evaluation of efficacy shows that the greater the difference (amplitude) between SpO_2 tension(breathing with a hypoxic mixture) and SpO_2 of rest (20.9 % O_2) during the session, then the more effective the training. Of course, the limits of these oscillations are determined.

Oxygen gives life, oxygen takes it. Without oxygen cells die. With too much oxygen cells die even faster. Mitochondria determine a cell's choice between life and death.With a high energy consumption by the cell, i.e. with greater delivery of glucose and oxygen, the mitochondria do not work efficiently and generate more superoxide (O-2). Superoxide is one of the active forms of oxygen (reactive oxygen species further referred to as ROS). ROS, under conditions of cellular stress, trigger and intensify the sequence of reactions that ultimately leads to cell death.The metabolism of all eukaryotes is based on the reduction of oxygen to water (O_2 to H_2O). This reduction of O_2 to H_2O can occur only with the formation of reactive oxygen species (ROS). ROS as "the signal for life" occurs under low concentrations of H_2O_2. A superoxide radical stimulates the division of normal cells in various tissues. On the other hand, H_2O_2 ROS and other ROS trigger the mechanism of cell death, the transformation of normal cells into malignant cells.

IHT, taking into account the doses which we use, can be called activation hypoxia, since it manifests itself as a physiological stimulus, and shows many well-known beneficial effects.

What are the key biochemical changes which stimulate the entire body system into giving a general response to moderate hypoxic effects? In a state of hypoxia, the body tends to produce the required amount of energy from a smaller amount of available oxygen. This is the main generalized, summing effect of this method.

First, there is an immediate synthesis of Hypoxia Inducible Factor (HIF-1), which allows the cells to adapt to hypoxic conditions. HIF–1 initiates many reactions aimed at improving the body's use of oxygen. HIF–1, a transcription factor that increases the expression of vascular endothelial growth factor (VEGF) and VEGF receptors, alters the expression of genes controlling glucose transport and glycolysis, leads to an increase in the expression of erythropoietin (EPO) genes, glycolytic enzymes, such as aldolase A, lactate dehydrogenase A gene, phosphofructokinase L gene and pyruvate kinase M gene. [24, 25].

HIF–1a is synthesized in various tissues, including nervous tissue [26]. It is found in all cells of the brain, but its expression in neurons is maximal. The synthesis of HIF-1a leads to an increase in the fowwlong: nitric oxide (NO), the synthesis of cytochrome-450, dopamine and serotonin, gamma-aminobutyric acid, thyroxine, insulin and improves the transport of glucose. IHT increases the stress-protein (caperone, shock protein) level in the cell [27]. There is an intensification of production and rejuvenation of mitochondria (a cell concentrator for the production of aerobic energy) and mitochondrial enzymes, which allows for more efficient use of oxygen for energy production and excellent enzymatic antioxidant protection.

Oxidative damage to mitochondrial DNA, mtDNA, is a recognized mechanism responsible for pathogenesis of aging in mammals. Progressive degradation of mitochondria underlies oxidative stress, which leads to an accumulation of molecular damage, genome instability, reduction of telomeres, metabolic disturbances, hormonal disorders and acceleration of glycosylation of proteins. Continuous renewal of mitochondria in somat-

ic cells can reduce oxidative stress, increase the efficiency of oxidative metabolism, slow down the aging process and prevent and/or retard the development of age-related pathologies.

The natural mechanism of mitoptosis, discovered in the mammalian organism, promotes the continuous purification of the mitochondrial basin in the body from damaged, old mitochondria. This actively produces free radical oxidation Reactive Oxygen Species (ROS). ROS include oxygen ions, free radicals and peroxides both of inorganic and organic origin. Oscillations of oxygen delivery eliminate the destroyed mitochondria and stimulate mitoptosis, which is the key to longevity [28]. Mitoptosis facilitates purification of the mitochondrial basin thus ensuring the spread of unmutated mtDNA.

IHT improves blood circulation and oxygen delivery to tissues due to the efficient operation of the ATP-K + pump. It was discovered that the ATP-K channels of intact ventricular cardiomyocytes blocked by intracellular ATP under normoxic ambient conditions begin to open in 20–25 minutes under moderate hypoxia. The dynamics of this activity has a periodic/cyclical rhythm [29].

One of the most effective factors of the biochemical environment of the body is nitric oxide (NO). NO acts on the smooth muscle walls of the vessels relaxing them. Nitric oxide also promotes the inhibition of the proliferation of smooth muscle cells. There is a decreased aggregation of platelets, leukocytes and erythrocytes; and reduction of adhesion of leukocytes to the endothelium. Nitric oxide induces neurogenesis and angiogenesis. Vascular growth occurs only where there is smooth musculature. This fact is important for solving the problem of the use of IHT in patients with cancer. As known, the vessels of cancerous tumors do not have smooth muscle tissue lining them. The synthesis of nitric oxide (NO) and its accessibility activates the expression of other protective factors, including the following: heat shock proteins [30], antioxidants, prostaglandins of H-synthase [31]. An adaptation to hypoxia prevents both NO overproduction and NO deficiency, resulting in an improvement in blood pressure [10, 11, 33]. IHT optimizes concentrations of nitric oxide by stimulating its synthesis, and also limiting its overproduction [32]. Understanding the role of NO in the mechanisms of the adaptation to hypoxia will help to substantiate the program for the prevention and treatment of hypoxia or ischemic damage to organs and tissues.

Hyperglycemia inhibits the formation of nitric oxide (NO) and weakens its effect. The lack of sufficient synthesis of NO under diabetes mellitus gives rise to a dysfunction of the endothelium, which in its turn leads to vasospasm, smooth muscle proliferation, activation/aggregation of platelets, and adhesion of leukocytes to the endothelium [34]. IHT is more effective when it is used for an organism under the conditions of normoglycemia or in a state of hunger. During and after fasting periods, sensitivity of receptors is increasing. Even morning fasts can play a positive role.

IHT improves oxygen delivery to tissues due to a change in hemoglobin, an increase in tissue affinity for oxygen. During IHT, hemoglobin binds to 2,3-DPG (2,3 diphosphoglycerate), which greatly facilitates the release of oxygen from hemoglobin into the tissue [35].

The uniqueness of hypoxic stimulation is that during IHT there is an improvement in blood circulation in that part of the body that is in the state of hypoxia. Affected or inflamed tissues and organs or parts of them have much lower pH, since they are in the state of hypoxia. IHT stimulates capillary dilation faster in tissues and organs where is much lower pH and an increased concentration of lactic acid (lactate) as compared to non-acidified, healthy ones. Thus, blood circulation improves primarily in the affected tissues and organs, including the brain. Therefore, the uniqueness of IHT stimulation makes it possible to treat not only wounds, trophic ulcers, lung abscesses, but also degenerative brain diseases: epilepsy, complex partial seizures, hyperkinesis symptoms, phantom pain syndrome, anorexia nervosa, depression, Parkinson's and Alzheimer's diseases [32].

The therapeutic effect can be achieved by improving oxygen delivery to the subcortical structures and, first at all, the nuclei of the visual hillock (median center, ventrolateral nucleus), or, in other cases, has the protective and therapeutic effect in survival of nigral dopaminergic neurons and in substantia nigra and striatum. As mentioned above, nitric oxide (NO) production plays an important role, and it is stimulated in the brain by erythropoietin.

IHT as an activation method acts on the whole organism and undoubtedly has much more advantages in achieving a quick and lasting result in increasing the overall resistance of the organism than the methods of action of individual adaptogenes. The im-

pact of IHT immediately involves the brain changing its blood circulation and biochemical status. It is known that even ordinary anxiety changes the blood circulation and biochemical status of the brain in a mosaic manner and/or locally [36], and it may be enough to have one IHT session to delete it. Practice showed this.

Patients with diseases such as epilepsy, depression, anorexia and many others, have a dominant, individual pathological mosaic pattern in the brain. These individual patterns demonstrate altered (insufficient) tissue respiration and altered nervous excitability, excessively accumulate certain metabolites, such as lactate (lactic acid). Undoubtedly, the same mechanisms work in the prevention and treatment of the consequences of strokes and heart attacks. Outstanding neurophysiologist Natalya Bekhtereva stressed that leaving the state of the brain unchanged we cannot cure a disease. The condition of a disease or a stable pathological condition, as Natalia Bekhtereva called it, is the "interconnected complex memory matrix" [37]. The mechanisms of its "erasure" and "re-education" are the improvement of blood circulation and tissue respiration, as well as the "cleaning" or removal of accumulated metabolites. Modes of "swinging" by the action of sparing point electrostimulation of the brain in the treatment of schizophrenia by Heath R.G. [38] are described in the 50's. Natalia Bekhtereva practiced treatment with electrical stimulation (TES) of the brain in case of hyperkinesis and phantom-pain syndrome, describing the treatment as "swinging". TES was effective if stimulation led initially to destabilization of painful manifestations, which was mentioned by V.M. Smirnov [39]. The repeated destabilization seems to be an activator and a trainer expanding the reserves of adaptation.

The "swing" with oxygen suggests a repeated shift in the amount of ROS, which, apparently, play not the least role in repetitive destabilization and subsequent adaptation.The metabolic shift occurs due to repeated changing in oxygen transport and leads to improvment of all the biochemical chains of oxygen delivery to the cells. An adaptation is a re-setting of the body in a new mode of operation, more sensitive, suppler and more flexible.

Such diseases as epilepsy, depression, anorexia and many others have of course their own individual patterns of altered blood circulation and biochemical state. The method of "re-education" for patients with epilepsy with the help of electrostimulation [16] can be completely replaced by IHT.

What studies confirm the antitumor effect of IHT on the body? IHT activates p53, a tumor suppressor. P53 (protein p53) functions as a suppressor of the formation of malignant tumors, respectively, the gene TP53 is an anti-oncogene. Mutations of gene TP53 are found in cells in about 50% of cancerous tumors. Often it is called the "guardian of the genome" [40]. Hypoxia regulates telomerase [41]. IHT improves blood circulation in organs and tissues by relaxing smooth muscles in capillaries, but not in cancerous tumors. Cancer does not contain smooth muscles in the vessels, so there is no embolization of the capillaries or improvement in blood circulation in tumors. Also, VEGF does not cause proliferation of smooth muscle cells (as well as corneal endothelial cells, lens epithelial cells, fibroblasts and adrenal cortex cells) [42,43].

What reactions can be observed in the patient's body immediately after IHT?

A positive response appears upon expiration of 15-30 minutes, the state of general calm manifests itself, often accompanied by relaxation and drowsiness, slowing down of breathing and heart rate. Some patients improve their color vision dramatically. Cheeks appear pink, limbs are warmed. After one or two sessions, sleep and mood improve. In some patients, long-term depression is cured. There is a comfortable feeling of relaxation in the stomach, "the lump in the throat or chest" often accompanies stress is gone. Digestion improves, and the nonspecific resistance of the body as a result of integral changes in the body increases.

Breathing gas mixtures with different oxygen content causes hypoxia of different levels and leads to various reactions by the body. A weak stimulus causes a training reaction, which leads to the accumulation of some substances (proteins, cells, tissues). A stronger stimulus induces the reaction of activation, which has some temporary destructive properties, but further leads to a more intensive synthesis of proteins and repair. A very strong stimulus initiates stress, which leads to a noticeable destruction and hinders the development of an adaptive response.

Strong, intense hypoxia, like other strong stimuli, causes stressful reactions of anxiety, resistance and oppression within 3 phases. Stressful reactions are accompanied by profound changes in the central nervous system, including the pituitary gland and its

hypersecretion of ACTH, suppression of the activity of the thymic-lymphatic system, metabolic disorders and high energy expenditure. As the founder of stress Hans Selye said, "protecting the body from a strong stimulus is achieved at a high price – at the cost of breakage and high costs." Stress is the nonspecific basis of any pathological process.

IHT makes it possible to purposefully dose the strength of stimuli and the amplitude of fluctuations of the hypoxic mixture. The purpose of IHT is to cause the development of general nonspecific reactions,which correspond to the symptom complex of an integral nonspecific adaptation activation or training reaction described and studied by Rostov scientists. [44–47]. It is important to take into account the individual sensitivity and subjective sensations of the individual (sleep, appetite, motor activity, efficiency, emotional state) and compare them with objective indicators.One of these can be a morphological blood test that classifies the strength of the impact and identifies the archetype of the reaction (training, activation, or stress) [48]. Monitoring heart rate variability (HRV) and studyingthe thermography of the body, an electroencephalogram (EEG) before the session and after it, dynamics of SpO_2 and breath-holding time may be utilized as valuable indicators for the assessments of treatment efficacy.

The methods of controlled enhancement of adaptation or activation acting on the whole body undoubtedly have many more advantages in achieving a quick and lasting result than methods of uncontrolled, blind effect of individual adaptogens.

Conclusions

Nature demonstrates that there are certain resources which can have a powerful and quick effect on metabolism.They can kill or cure. Considering them, oxygen is among the strongest.Our aim is to design, develop and apply the most efficient IHT methodology to act as a natural trainer, regulator and activator for restoration and rejuvenation for the body and brain.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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