Effectiveness of Intermittent Hypoxia–Hyperoxia Therapy in Different Pathologies

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Intermittent oxygen therapy (IHT), initially used in the hypoxic administration variant, has been shown to be effective in various pathologies studied, from cardiopulmonary to vascular and metabolic pathologies and more. IHT used to prevent and treat various diseases has thus gained more and more attention as the years have passed. The mechanisms underlying the beneficial effects have been investigated at multiple biological levels, from systemic physiological reactions to genomic regulation. In the last decade, a new method of intermittent oxygen therapy has been developed that combines hypoxic and hyperoxic periods. They can be applied both at rest and during physical exercise, hence the specific indications in sports medicine. It has been hypothesized that replacing normoxia with moderate hyperoxia may increase the adaptive response to the intermittent hypoxic stimulus by upregulating reactive oxygen species and hypoxia-inducible genes.

Keywords: intermittent hypoxia hyperoxia ; training ; physical exercise ; rehabilitation

1. Introduction

Intermittent hypoxia (IH) is generally defined as repeated episodes of hypoxia interspersed with normoxic episodes. Experimentally repeated short-term hypoxia (about 5 min) with normoxic intervals has been used by Russian doctors for many years [1]. The first steps in the use of intermittent hypoxia training (IHT) were for the training of athletes, climbers and pilots. Research conducted in 1939–1943 showed that even a small height improves pulmonary ventilation and increases hemoglobin concentration and oxygen saturation. Research at the time also drew attention to the possible curative effects of hypoxic adaptation [2]. Thus, intermittent hypoxia training (IHT) was initially recognized in sports medicine as a potentially useful strategy for improving exercise performance in athletes. In addition to improving physical performance and preclinical protective effects of IHT, it has been considered in healthy subjects to be potentially useful for improving physiological functions as well [3]. IHT is the emerging therapeutic modality for the prevention and treatment of various diseases, gaining increasing attention in recent years [4].

Increased exercise tolerance in patients with cardiovascular, bronchopulmonary and metabolic syndromes improved cardiometabolic status in elderly patients and increased cognitive potential in Alzheimer's disease and in clinical observations; all of these achieved with the help of IHT have been demonstrated by several studies throughout the years [5].

Medical protocols for intermittent hypoxia therapy have been developed, with this therapy advancing rapidly in modern times. They use mild, non-harmful hypoxic training that provides benefits and drug-free treatment for several chronic degenerative pathologies [6].

In the last decade, intermittent hypoxia–hyperoxia training (IHHT) has entered medical practice, and periods of breathing atmospheric air have been replaced by breathing a hyperoxic gas mixture [7]. A new training method has been suggested, IHHT (intermittent hypoxia–hyperoxia training), which uses hyperoxic intervals instead of normoxic ones between hypoxic breathing sessions. The patient receives a gas mixture containing 30–40% O_2 in the mask. The efficacy, safety, and tolerability of IHHT have been demonstrated in placebo-controlled pilot clinical trials [8].

Periods of intermittent hypoxia–hyperoxia can be applied as a passive intervention with patients at rest (IHHE—intermittent hypoxic–hyperoxic exposure) or during exercise (IHHT—intermittent hypoxic–hyperoxic training). Intermittent hypoxia–hyperoxia, either passive or in combination with exercise, appears to be a promising therapeutic strategy for various populations [9].

2. Effectiveness of Intermittent Hypoxia–Hyperoxia Therapy in Different Pathologies

Intermittent hypoxia–hyperoxia training (IHHT) can bring important benefits in improving the symptoms and functionality of patients with various cardiovascular, respiratory, musculoskeletal, neurological, and metabolic pathologies and also geriatric patients with multiple comorbidities. These patients may have contraindications to multimodal therapy, which also includes physiotherapy, considering that many of them have multiple organ failures (kidney, liver, and heart failure) [10][11].

Published studies demonstrate that IHHT brings superior improvements to multimodal therapy (physiotherapy, physical therapy, and occupational therapy), demonstrating its effects at the biological and molecular level, but also at the functional level, of the cardiorespiratory fitness and cognitive status of the patients [5][12].

Specific systemic mechanisms of adaptation to hypoxia include changes in the functioning of the cardiovascular system that increase oxygen delivery to tissues in need, changes in pulmonary ventilation and changes at the tissue level that allow more efficient use of oxygen for metabolic processes. Specific reactions to hypoxia are accompanied by an increase in the blood level of glucocorticoids. This adaptive response provides increased resistance to hypoxia and many other environmental factors [13].

Combining hypoxia and hyperoxic breaks in one procedure has a good physiological basis in the hypoxic–hyperoxic paradox hypothesis. Hypoxia is a natural trigger of mitogenesis and mitochondrial metabolic changes by inducing hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), other relevant molecular cascades, stem cell proliferation, etc. Hyperoxic stimuli accompanied by increased oxygen availability promote the production of both reactive oxygen species (ROS) and ROS scavengers and trigger the same molecular cascades as hypoxia, activating angiogenesis, mitogenesis, oxidative phosphorylation (OXPHOS) efficiency and metabolic activity in various tissues [14].

Acute hypoxia causes mitochondrial swelling, organelle vacuolization and disorganization and destruction of mitochondrial membranes. Exposure to IHT causes an increase in the total number of mitochondria, a reduction in the number of structurally modified organelles, the appearance of energetically active Mt with vesicular cristae and the formation of micromitochondria (microMt). Excessive production of reactive oxygen species (ROS) in the mitochondria that oxidize proteins, lipids and DNA is an important mechanism of cell damage during hypoxia and reoxygenation. The low level of ROS production is protective and serves as a trigger for adaptive responses. IHT leads to the reprogramming of mitochondrial metabolism, ensuring adequate ATP production. Activation of potassium transport in the mitochondrial matrix under IHT is a protective mechanism against Ca^{2+} overload caused by acute hypoxia. All hypoxia adaptation reactions are regulated by HIF factors (HIF-1, HIF-2 and HIF-3). Each of the HIF subunits plays a specific role depending on the mode of hypoxia-induced stress [15].

The 2019 Nobel Prize in Physiology or Medicine was awarded to three physician scientists, Drs. William G. Kaelin, Jr., Peter Ratcliffe and Gregg Semenza, for their groundbreaking work revealing how cells sense and adapt to oxygen availability [16].

In 1995, Dr. Guang-Liang Wang and Dr. Bing-Hua Jiang purified and cloned this transcription factor, which they named hypoxia-inducible factor-1 (HIF-1). HIF-1 is composed of two subunits, HIF-1α and HIF-1β. Despite the fact that mRNA expression of both subunits typically remains constant in either normoxia or hypoxia, the HIF-1α protein was found to be induced and accumulate in hypoxia, suggesting that some type of post-transcriptional/post-translational modifications contribute to the regulation of HIF-1α at the protein level [16].

Biological responses to intermittent hypoxia can be either adaptive or maladaptive, depending on the severity, frequency, and duration of hypoxemia. The different detrimental versus beneficial effects of intermittent hypoxia may depend on the different number of hypoxia episodes, severity and total exposure duration of hypoxia, which may mobilize the body's adaptive mechanisms or cause dangerous pathological processes in more severe or prolonged hypoxia events. Potential beneficial effects of IHT on the human cardiovascular system have been either experimentally demonstrated or proposed, including the following: increased myocardial metabolic processes, increased myocardial tolerance to ischemia-reperfusion injury, reduction in free radical damage at the cellular level, development of endothelial function and microcirculation, positive inotropic effect on cardiac function, normalization of blood pressure, reduction in sympathetic nervous system activity, limitation of blood viscosity and platelet aggregation [17].

Low doses of IH upregulate hypoxia-sensitive growth/trophic factors within respiratory motoneurons but do not cause detectable pathologies such as hippocampal cell death, neuroinflammation or systemic hypertension. Progress has been

made in understanding the cellular mechanisms that give rise to IH-induced respiratory plasticity, and attempts have been made to harness the benefits of low-dose IH to treat respiratory failure after cervical spine injury [18].

In 2014, Wang et al. designed a study in which they followed weight loss in obese adolescents by exposure to IH for 4 weeks together with physical training and dietary intervention. They intended to include in the study 40 obese girls and boys aged between 11–15 years. They were to be assigned to the control group (sleep under normal conditions) or the hypoxia group (sleep in a normobaric hypoxia room). The results could lead to a potential utility of IHT in a weight loss program among obese children and adolescents [19].

Humans or rodents exposed short-term to moderate isocapnic hypoxemia (SaO_2 75–80%) daily sessions for several weeks, with 10–15 episodes lasting 1–2 min alternating with an equal duration of normoxia, may benefit without maladaptive cardiovascular sequelae. The improvement of ventilation in rodents and humans with spinal cord injuries can be achieved with this type of noncyclic, short-duration, mild-severity IH, which induces respiratory motoneuron plasticity, followed by a progressive increase in phrenic and hypoglossal nerve [20].

Another important concept of adaptation to intermittent hypoxia is its impact on extracellular adenosine generation and signaling. Adenosine belongs to the group of molecules called purines. Purines are some of the most influential and oldest biochemical compounds in the history of evolution. Alan Drury and Albert Szent-Györgyi of the University of Cambridge suggested in 1929 that purines might also function as extracellular signaling molecules. In many studies, it is suggested that extracellular adenosine comes mainly from the breakdown of precursor nucleotides (for example ATP—adenosine triphosphate) under certain conditions such as hypoxia, inflammation or ischemia. The hypoxia–adenosinergic signaling pathway can be targeted to make cancer-adoptive immunotherapy, according to Sitkovsky et al. Dr. Colgan's studies implicated inflammatory hypoxia in the extracellular production and control of adenosine signaling and identified hypoxia-induced increases in adenosine signaling as a control mechanism for attenuating intestinal inflammation, as occurs during inflammatory bowel disease [21].

To understand the interactions between PMNs (polymorphonuclear leukocytes) and the vascular endothelium and to identify potential therapeutic targets to limit the vascular leakage syndrome associated with inflammation and hypoxia, the first step is to identify the biological mechanisms that control endothelial barrier function and regulate vascular leakage. Hypoxia is a common feature of inflamed tissues, accompanied by significantly increased levels of adenosine. The exact source of adenosine is not well defined, but it may result from a combination of increased intracellular metabolism and the enhanced extracellular phosphohydrolyzing of adenine nucleotides by surface ecto-nucleotidases [22].

Hypoxia-inducible factors (HIFs) are found in inflammatory conditions and diseases, including inflammatory bowel disease, pathogen infection, acute lung injury and myocardial injury, or during ischemia-reperfusion injury. Hypoxia and inflammation are closely related: at the cellular level, hypoxia can cause inflammation, and inflammation can cause hypoxia. Although hypoxia can be an inflammatory stimulus that encourages pro-inflammatory responses and destroys tissue barriers, there are many examples where stabilization of HIFs induces anti-inflammatory and tissue-protective responses [23].

MicroRNAs (miRNAs—micro ribonucleic acid) are considered to be functionally involved in almost all physiological processes, including differentiation and proliferation, hemostasis, metabolism, apoptosis and inflammation. Transcriptional regulation of miRNA expression can be controlled by classical transcription factors. In hypoxia, the hypoxia-inducible transcription factor (HIF) is stabilized and has been shown to regulate a group of miRNAs. The interactions between miRNA and HIF are feedback loops that are relevant to cellular processes such as proliferation, cell cycle progression or angiogenesis, processes that play a role in tumorigenesis but also in ischemia-reperfusion [24].

Despite the wide range of possible effects on various pathological conditions (**Table 1**), IH is not routinely prescribed or widely used. Future studies on larger populations on the efficacy and long-term effects of IH are needed in order to gain more evidence for further recommendations.

Table 1. Effects of intermittent hypoxia—IH—on different clinical conditions [21].

Pathology	Effect Observed
Chronic obstructive pulmonary disease	**In randomized, double-blind, controlled clinical studies it was demonstrated that mild repetitive acute IH (12–15% O2 for 3–5 min, followed by intervals of 3–5 min of normoxia, 5–9 episodes per day, for 15 days) can produce the following increases: exercise time, baroreflex sensitivity, total hemoglobin, hypercapnic ventilatory response, forced vital capacity and forced expiratory volume in 1 s.**

Pathology	Effect Observed
Arterial hypertension	**In 56 known patients with stage I-II hypertension, moderate IH reduced heart rate, systolic and diastolic blood pressure and peripheral resistance. IH reduces the symptoms of angina, normalizes microcirculation and lipid metabolism and increases maximal oxygen consumption and exercise tolerance, being proven to be a safe therapy for elderly patients. Increased endothelial NO production that produces the opening of reserve capillaries and vasodilatation can determine the antihypertensive effects of moderate IH (reduced peripheral resistance), reduced sympathetic activity, minimized calcium overload of vascular smooth muscles, improved water and salt metabolism, increased activity of antioxidant enzymes and increased synthesis of angiogenic growth factors, including VEGF and FGF.**
Myocardial Infarction	**In humans, moderate IH increases maximal oxygen consumption in older men (50–70 years), both with and without coronary artery disease. During submaximal exercise (cycling at 1 W/kg), systolic blood pressure, heart rate, perceived exertion and blood lactate concentration are diminished by IH. Myocardial protection is correlated with the ability of moderate IH to increase coronary blood flow, myocardial vascularity, cardiomyoglobin and antioxidant enzyme expression. IH increases erythropoietin (EPO) concentrations, stimulating erythropoiesis and increasing hematocrit, blood viscosity and platelet count.**
Inflammatory/immune responses to IH	**Some studies suggest that moderate IH protocols enhance the innate immune system while having a general anti-inflammatory effect. For example, in healthy humans, exposure to the 4 5 min episodes of 10% O_2 (5 min interval in room air, 14 days) increases the phagocytic and bactericidal activities of neutrophils, while suppressing the pro-inflammatory mediators TNF-α and IL-4 by more than 90%. These responses, which persisted at least 7 days after IH, may increase the body's immune defenses without associated inflammation.**
Metabolic responses to IH	**IH protocols have beneficial effects on metabolism, including decreased body weight, cholesterol, and blood sugar levels, as well as increased insulin sensitivity. Mechanisms of moderate IH-induced weight loss may include increased serotonin and/or leptin levels. Body weight is reduced with moderate IH by increasing hepatic leptin expression and increasing blood leptin concentration. Moderate hypoxia (14.6% O_2) reduces cholesterol and blood glucose and increases insulin sensitivity in patients with type 2 diabetes. Hypoxia also increases glycolysis and fatty acid oxidation and mitochondrial enzyme activity and reduces cholesterol synthesis.**
Bone	**IH has positive effects on bone tissue remodeling. Exposure of rats to IH determined high alkaline phosphatase activity in bone tissue, thus suggesting increased osteoblast activity and new bone formation.**

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