УДК 616-035
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PHYSIOLOGICAL EFFECT OF BIOFEEDBACK-CONTROLLED INTERVAL HYPOXIA-HYPEROXIA TREATMENT IN HUMANS

While adverse effects of tissue hypoxia are well-known and are implicated as key pathological mechanisms in a variety of disorders ranging from ischaemic heart disease and stroke to sleep apnea, beneficial adaptational effects of mild normobaric hypoxia applied in brief intervals within the physiological compensation zone are gaining attention as the new effective method of treatment and prevention of the very same conditions where hypoxia shapes and defines pathogenesis. In addition, such hypoxic preconditioning is gaining popularity in sports medicine as a safe doping-free way of improving sportsmen performance and accelerating recovery from overtraining.

Major compensatory mechanisms to mild hypoxia can be divided into two major categories: transient effects due to activation of sympathetic tone (e.g. brief increase in heart rate), and long term adaptational changes at all systemic levels which lead to improved oxygen transport and utilisation, and are responsible for building up therapeutically useful hypoxia resistance. Such changes are predominantly, but not exclusively, linked to activation of the hypoxia-inducible factor-1 (HIF-1): a transcription factor which activates over 300 genes after translocation to the nucleus under hypoxic conditions. The most relevant HIF-1 activation effects are outlined and include NO-mediated vasodilatation (lowering blood

pressure in hypertension without a significant effect in healthy humans), revascularisation (essential in promoting myocardial infarction and stroke recovery), erythropoiesis (useful in treatment of anemias and in sports training), and optimisation of anaerobic metabolism (effective in treatment of type 2 diabetes, metabolic syndrome, and in sports/fitness/weight loss training programs).

However, to reach clinically significant effects interval hypoxia treatment (IHT) where a patient returns to normoxia after a brief 3-5 min hypoxia period has to be performed for a long time (at least 20-25 treatment sessions), which is often unfeasible taking into account realistic hospitalisation terms. Trying to enhance the effect by increasing hypoxia depth is risky as the patient may enter critical hypoxia zone where adverse effects will overwhelm their adaptational counterparts. In addition, physiological responses to hypoxia are highly individualised (alas being partially predictable by results of preliminary Shtange and Genchi-Sabraze tests), which can also lead to less predictable beneficial and even side effects.

To overcome these limitations, we have developed a novel method of IHT where the patient is returned to a brief period of hyperoxia (up to 45 % O2) instead of normoxia, and the treatment is precluded by an automated hypoxia test to determine individual sensitivity and starting safe hypoxia level. During the entire exposure, concentration of O2 in the inhaled air is adjusted in real time via biofeedback measuring both SpO2 and heart rate. This approach, implemented in our ReOxyTM device, has allowed to shorten both the session time due to faster subject reoxygenation, and the number of sessions (from 20-25 to 10-12) needed to reach detectable clinical effects. Besides, the new method was better tolerated by patients as compared to hypoxia-normoxia exposure only. More interestingly, apart from building tolerance to hypoxia, interval hypoxia-hyperoxia treatment (IHHTTM) provided by ReOxyTM promotes conditioning to oxidative stress, via activation of physiological antioxidant defences (e.g. superoxide dismutases and catalases). This is essential for treatment and prevention of

disorders where both hypoxia and oxidative stress play critical role, such as in ischaemic stroke where oxidative stress develops due to metabolic failure and resulting excitotoxicity. Paradoxically, brief interval hypoxia and hyperoxia appear to be synergistic. At a high level, this can be explained by return to normoxia from hypoxia having hyperoxia-like effects, and return from hyperoxia to normoxia having hypoxia-like effects. At cellular and molecular levels, a variety of mechanisms underlying interval hypoxia and hyperoxia effects actually converge, or are the same.

In addition, mounting evidence that reactive oxygen species (ROS) signalling (particularly triggered by mild hyperoxia) stabilise HIF-1 alpha hence enhancing its effects is remarkable.