INTERMITTENT HYPOXIA: MECHANISMS OF ACTION AND SOME APPLICATIONS TO BRONCHIAL ASTHMA TREATMENT

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ABSTRACT

Being essentially cut off from the global scientific community, Ukrainian and Russian scientists have developed a new concept for the beneficial use of adaptation to artificial intermittent hypoxia in treating of many diseases. The basic mechanisms underlying intermittent hypoxic training were elaborated mainly in three areas: regulation of respiration, free radical production and mitochondrial respiration. Twenty-year experience of the application of intermittent hypoxic therapy for the treatment of chronic obstructive bronchitis and bronchial asthma allows affirming that the adaptation to this kind of hypoxia causes a significant improvement of the clinical picture or even a complete recovery. The absence of negative side effects, typically observed during drug therapy, and the stimulation of organism's general, nonspecific resistance, makes the hypoxic therapy a treatment with a future. A special note is devoted to the use of intermittent hypoxic training in industrial health care for the purpose of prophylaxis and treatment of professional diseases.

Key words: *bronchial asthma, intermittent hypoxic training, hypoxia, respiratory adaptation*

INTRODUCTION

The problem of hypoxia is a multi-headed Medusa in physiology and clinical medicine. Two main aspects of this problem are hotly discussed: the destructive and the constructive action of hypoxia. One viewpoint belonging primarily to western scientists is perfectly expressed in Barcroft's words: "Hypoxia not only intercepts the machine, but also damages the mechanism". The second veiwpoint, expressed primarily by the former Soviet Union (FSU) scientific schools, reads as follows: "Hypoxia (even severe but brief and intermittent) can cause beneficial effects on an organism". However, many a scientific publication was in Russian or Ukrainian and because they were not widely available in other countries, these research findings remained obscure. The purpose of this review is to summarize some past and recent achievements in the field of intermittent hypoxic training (IHT), giving special consideration to applied problems in the treatment of bronchial asthma (BA).

Historical aspects

Historically, first steps in the use of IHT were for training pilots, mountaineers and athletes. The pioneering research, carried out in 1939-1943 (see 1 for review), showed that even a small altitude elevation produces positive adaptation effect, improving lung ventilation and increasing hemoglobin concentration and arterial oxygen saturation. The research of the time drew attention not only to constructive and creative hypoxic training but also to possible curative effects of hypoxic adaptation. More than 30 years later, other studies have shown that a training protocol that includes gradual adaptation to hypobaric hypoxia improves the working capacity and endurance of athletes and astronauts. Inhalation of hypoxic gas mixtures to produce IHT was rapidly introduced into sports training and diseases treatment procedures. IHT protocols and equipment were devised and manufactured for this purpose.

MATERIAL AND METHODS

Two methods are used to produce IHT in the FSU countries: (i) barochamber hypobaric hypoxia (including altitude hypoxia) and (ii) normobaric hypoxia. Historically, IHT was first performed using a barochamber. A number of observations were made in both animals and humans using this method (2, 3), despite negative sequelae of compression/decompression that accompanied immediate positive effects of hypobaric therapy. Currently, normobaric hypoxic protocols, outlined below, are commonly used.

- Hermetic cabin for 5-7 subjects, where oxygen concentration is maintained between 16-13% and temperature between 15-16°C. Each session lasts 30-60 min once a day over 15-20 days (4).
- Hypoxic device for one individual, working on the open breathing system principle. The patient breathes through a mask or mouthpiece into an open circuit (5, 6). He inspires alternately hypoxic mixture (16-12 %) and atmospheric air for 3-10 min. The procedure is repeated 5-10 times a day over 15-20 days. Hypoxic mixture is produced with a polymer membrane-selective permeability method for separation of gas molecules.
- Rebreathing technique with CO_2 absorption (7, 8) for one individual. Here, a patient can breathe to his individual tolerable limit (usually down to 10-7% O_2) or to a fixed level (usually 12-9% O_2). When the oxygen concentration reaches the set level (depending on the age and type of disease), this level is maintained for 5 min. Generally, three sessions are administered each day at 10-20 min intervals for a period of two weeks.

Each of these modifications has its advantages and disadvantages. It is worth noting that authors use quite different protocols (gas concentrations, duration and number of sessions, length of treatment) in the animal experiments or treatment of humans. This lack of standardization introduces variability that makes comparisons of results difficult.

RESULTS AND DISCUSSION

Mechanisms

The basic mechanisms underlying the beneficial effects of IHT were elaborated mainly in three areas: (i) regulation of respiration, (ii) free radical production, and (iii) mitochondrial respiration (see 1 for review). Findings showed that IHT induces increased ventilatory sensitivity to hypoxia and other hypoxia-related physiological changes. Due to IHT, cellular membranes become more stable and improvement of O_2 transport in tissues is evident. IHT induces changes in mitochondria, involving NAD-dependent metabolism, which increases the efficiency of oxygen utilization in ATP production (9). These effects are mediated partly by NO-dependent reactions (3, 10). NO-dependent reactions are especially important for investigations of bronchial asthma (BA) pathogenesis, because exhaled nitric oxide is related to actual levels of airway inflammation in asthmatic patients. There are pieces of evidence that IHT may actually decrease the pronouncement of tissue hypoxia and intracellular acidosis under acute hypoxic exposure, improve O_2 transport in tissues, increase oxidative metabolism enzyme synthesis and ion-transport systems in cell membranes, and rearrange the cell membrane phospholipid composition. IHT also seems to increase tissue capillary growth. Meerson (2) has opined that positive IHT effects are based on the cross-protective values of adaptations to one stress providing resistance to another stress.

The influence of IHT on free radical process seems of key significance, as these processes are implicated in the pathogenesis of BA. Alveolar macrophages, blood neutrophils and eosinophils from asthmatic patients have been shown to release more oxygen radicals than those from healthy subjects do. Radicals induce airway hyperreactivity, destruction of lung epithelial cells, mucus hypersecretion, platelet-activating factor synthesis, and other reactions typical for BA in humans and animals (11, 12). These unwanted changes are underlain by tissue hypoxia and consequent reduction of electron transfer in the respiratory chain, an increase of functional activity of inflammatory cells, and by inhibition of antioxidant defense systems. IHT acts positively on these three mechanisms eliminating tissue hypoxia, normalizing the number and phagocytic activity of white blood cells and enhancing antioxidant enzyme activity (13). During IHT, the periods of reoxygenation lead to oxygen radical formation, which might be analogous to that occurring with normoxic reperfusion of transiently hypoxic or ischemic tissues. If periods of hypoxia followed by normoxia lead to the formation of oxygen radicals, and the hypoxic periods are much briefer than normoxia, and if this exposure sequence is repeated over a number of days, then antioxidant defenses will be enhanced much more effectively than in the condition of sustained hypoxia.

There are studies suggesting that adaptation to IHT increases antioxidant defense potential, accelerates electron transport in the respiratory chain, augments Ca^{2+} elimination from the cytoplasm, and stabilizes cellular membranes. Such studies have introduced IHT as a treatment modality in various diseases in which free radical outbreaks are anticipated, among them, in BA.

Clinical studies on hypoxic training in bronchial asthma

The largest number of clinical investigations devoted to the use of IHT for disease treatment is concerned with BA and chronic obstructive bronchitis (COB).

IHT has been used for these diseases for more than two decades. Among hundreds of reports, we have chosen just few to illustrate the achievements of IHT.

Donenko (14) has reviewed an 8-year long use of a hypobarochamber for the treatment of 1000 patients with COB and BA in a regional hospital. The treatment had both positive and negative effects. Positive results were shown in brief preliminary clinical trials. Significant decreases in the feelings of shortness of breath (SOB) and chest congestion were noted during the first session. But the patient status quickly returned to the pre-treatment state after the session had ended. Further treatments led to steady subjective improvements. IHT positively affected the psycho-emotional state of patients. They liked the procedure and asked, in cases of relapse, about further treatment in the barochamber. The author repeatedly observed an interruption of nascending asthmatic fits in BA patients. The improvement was recorded to occur at a simulated altitude of 2000-2500m. Kulberg (15) has reported similar findings. Barochamber training (3500m, 1 hour per day for 25 days) resulted in the disappearance of asthmatic fits in 72% of children and facilitated improvement in another 20% of them when combined with the drugs asthmopent or euphillin. Only did 8% of asthmatic children not respond favorably to IHT.

Nevertheless, barochamber therapy has some significant disadvantages. Primarily, hyperbaria is linked to negative effects on organisms. Tolerance of an individual to hypobaric hypoxia is 4 times lower than that to normobaric hypoxia (5). Barochambers are hardly accessible to practical health care due to the cost and complicated determination of a proper individual dosage. Thus, normobaric training has recently attracted more attention. Donenko (14) reported that during normobaric hypoxic therapy only 6% of 93 patients displayed intolerance to the procedure. In BA patients, a very good effect was noted in 58%, satisfactory in 38%, and no effect in 4%.

The IHT treatment (mixtures of 11-14% O_2) of COB and chronic pneumonia during remission, in both adults and children, significantly improved the clinical picture. Cough was diminished or disappeared and the amount of sputum was reduced and its expectoration was facilitated (3). However, it was impossible to completely stop disturbances of the aerodynamic properties of bronchial pathways in patients with an advanced broncho-obstructive syndrome in 10-12 sessions of therapy. The course of treatment was prolonged until positive effects were achieved in these patients. In cases of valve-type bronchial patency disturbances associated with a collapse of small bronchi during expiration, extension of the treatment for up to 20 days produced significant improvements.

Similar results were obtained in other studies (16, 17). Anokhin et al. (18) performed a normobaric hypoxic stimulation (4 sessions of 12-15% O_2 for 5 min alternating with 5-min rest intervals, for 10 days) in 200 children aged 4-14 who suffered from BA and compared the results with those in a sham group. A positive effect was seen in 85% of subjects in the hypoxic group and in 25% in the sham group. In children with mild BA, complete discontinuance of wheezing attacks was observed. In patients with medium-severe forms, a partial improvement was noted consisting of fewer attacks at less medicine use. In patients with severe forms, a small improvement was noted. The lowest efficacy of IHT was noted in children with an infection-dependent form of BA (17, 19). A positive clinical effect in patients with mild and medium atopic BA was sustained for an average of 4 months following hypoxic therapy. IHT in children with BA can be performed only in between, and not during, the exacerbations. In the hormone-dependent form of BA, IHT gives unsatisfactory results (5, 17, 19).

The use of a rebreathing method, twice a day for 10-15 days, results in a stable abatement of obstructive symptoms. The course of such a treatment is shorter in comparison with the investigations outlined above due to the individual selection of the end-attainable level of hypoxia in each patient. Karash et al. (5) delineated three groups of patients with respect to the sustainability of positive effects: (i) improvement of the condition for at least 1 year or more (54%), (ii) improvement lasting up to 6 months (29%), and (iii) positive effects lasting 1-4 months after treatment (17%). In 5% of patients, an appreciable improvement comes only after repeated courses of IHT. More than half the patients with a positive effect of the first course of IHT, reported further improvements with sequential courses of the therapy. Individual differences in respiratory reactions to hypoxia, from ventilatory hypersensitivity to complete absence of reaction, should be taken into account when designing IHT (6, 19). To wrap it up, experimental and clinical evidence has laid the groundwork for a wider use of IHT in the treatment of BA and other respiratory diseases.

Use of hypoxic training in industrial health care

A special note is in place about the use of IHT in industrial health care for the purpose of prophylaxis and treatment of diseases in professions dealing with harmful products. The respiratory system has been under investigation within the industrial network. Karash at al. (5) described IHT use for health recovery of textile plant workers. The training regimen was 3-5 min of breathing 10% O_2 with 3-5 minute breaks, beginning with 4 sessions per day and working up to 10 session per day over 15-20 days. The training group was 132 workers with 50 people subjected to sham training. The efficacy of treatment was determined by the number of missed days of work. The results showed reduced morbidity rates by 45.6%, reduced number of sick leaves by 49.5%, and reduced plant benefits per 100 sick persons per year by 44.5%.

Berezovsky et al. (20) investigated the effects of an artificial mountain climate on respiration and blood circulation in coal miners suffering from chronic dust bronchitis. The normobaric hypoxic chamber was used for treatment. Miners underwent hypoxic exposure for 1 hour a day for 12 days. The consecutive daily regimens of IHT were: equivalent to 3000m, 4000m, 5000m, and 6000m altitudes. IHT caused significant improvements in respiration, oxygen utilization, oxygen transport through the air-blood barrier, and in the feeling of well-being and it diminished chronic bronchitis symptoms. These and many other data strongly suggest the effectiveness of IHT in industrial health care.

In conclusion, hypoxic training represents a promising field of study in prevention and treatment of many diseases. The proper choice of the hypoxic dosage depends on an individual's reactivity and should be titrated for each patient to avoid negative side effects and to augment a favorable outcome. The absence of negative side effects, typically observed during drug therapy, and the stimulation of organism's general, nonspecific resistance, makes the hypoxic therapy a treatment with a future.

REFERENCES

1. Serebrovskaya TV. Intermittent Hypoxia Research in the Former Soviet Union and the Commonwealth of Independent States (CIS): History and Review of the Concept and Selected Applications. *High Alt Med Biol* 2002; 3: 205-221.
2. Meerson FZ. Adaptation to intermittent hypoxia: mechanisms of protective effects. *Hypoxia Med J* 1993; 3: 2-8.
3. Manukhina EB, Mashina SYu, Smirin BV et al. Role of nitric oxide in adaptation to hypoxia and adaptive defense. *Physiol Res* 2000; 49: 89-97.
4. Berezovskii VA, Levashov MI. Introduction in Orotherapy. Academy of Hypoxia Problems of Russian Federation, Kiev, 2000; p. 75.
5. Karash YuM, Strelkov RB, Chizhov AYu. Normobaric hypoxia in treatment, prophylaxis and rehabilitation. Moscow, Meditsina, 1988; p. 352.
6. Tsvetkova AM, Tkatchouk EN. Hypoxia user - the opportunity of individual programming of interval hypoxic training. In Hypoxia, Mechanisms, Adaptation, and Correction. Moscow, BEBIM, 1999; pp. 83-84.
7. Nemerovskii LI. Principles of the design of the equipment for intermittent normobaric hypoxia. *Med Tekh* 1992; 1: 3-8.
8. Serebrovskaya TV, Roitman EM, Lopata VA, Osaulenko VL, Lipkan OE. Device for breathing with hypoxic mixtures "Hypoxydoz". Patent of the Ukraine 2002054442, 2002.
9. Kurhalyuk NM, Serebrovskaya TV, Kolesnikova EE. Role of cholino- and adrenoreceptors in the effects of intermittent and acute hypoxia on rat liver mitochondrial respiration. *Ukr Biochim J* 2002; 74: 111-116.
10. Kurhalyuk NM, Serebrovskaya TV. Intermittent hypoxic training influences on antioxidant enzymes activity and lipid peroxidation under acute hypoxia and nitric oxide donor treatment. *Med Chem* 2001; 3: 69-71.
11. Serebrovskaya TV, Mankovskaya IN, Serebrovskaya ZA, Oberenko OA, Belinskaya IV. The effect of intermittent hypoxic exposure on free-radical processes and antibacterial system defense in bronchial asthma. *Hypoxia Med J* 1994; 2: 64.
12. Prasad K, Gupta JB. Relaxant effect of oxygen free radicals on rabbit tracheal smooth muscle. *Pulm Pharmacol Ther* 2002; 15: 375-84.
13. Serebrovskaya TV, Safronova OS, Gordiy SK. Free radical processes under different oxygen supply conditions. *Fiziol J*, 1999; 45: 92-104.
14. Donenko YuI. Comparison of intermittent normobaric hypoxic therapy and hypobaric therapy in treatment of chronic nonspecific lung diseases. In Intermittent Hypoxic Training-Effectiveness and Mechanisms of Action. Kiev, Institute of Physical Culture, 1992; pp. 65-68.

15. Kulberg AYa. Regulation of the Immune Response. Moscow, 1997; pp. 148-157.
16. Kolchinskaya AZ, Hatsukov BH, Zakusilo MP. Oxygen Insufficiency: Destructive and Constructive Actions. Nalchik: Kabardino-Balkaria Scientific Center, 1999; p. 207.
17. Chizhov AI, Bludov AA. Efficiency of intermittent and resonance intermittent normobaric hypoxia therapy in patients with infection-dependent bronchial asthma. *Vestn Ross Akad Med Nauk* 2000; 9: 48-50.
18. Anokhin MI, Geppe NA, Dairova RA. Effects of hypoxic stimulation observed in the animal experiments and in children with bronchial asthma. *Fiziol Zhurn* 1992; 38: 33-39.
19. Ehrenburg IV, Kordykinskaya II. Effectiveness of the use of intermittent normobaric hypoxia in treatment of chronic obstructive lung diseases. In: Intemittent Hypoxic Training- Effectiveness, Mechanisms of Action. Kiev, Institute of Physical Culture, 1992; pp. 96-98.
20. Berezovsky VA, Deinega VG, Nosar VI, Bogomolerz VI. Effect of artificial mountain climate on respiration and blood circulation in coal-miners suffering from chronic dust bronchitis. *Fiziol Zhurn* 1985; 31: 619-623.

Different spellings of the authors' names may be present in the English language literature.