INTERVAL HYPOXIC THERAPY/ TRAINING

Adaptation to interval normobaric hypoxia has been demonstrated to provide beneficial results in a wide spectrum of diseases and health related conditions.

The principle of Interval Hypoxic Therapy/Training (IHT) is based on alternation of multiple brief exposures to normobaric hypoxia (breathing in a hypoxic gas mixture using a mask) and subsequent reoxygenation (normoxia - breathing in ambient air). IHT regimens are customised individually depending on the IHT purpose and the functional state of the patients. An IHT session consists of alternating periods of hypoxia (PiO2 - 9-14 kPa corresponding to 9-14% O2 at sea level) - reoxygenation, each period lasting 2-15 min, 5-10 periods per each session, one session per day, 10-30 sessions per each course.

What is hypoxia? Hypoxia is less oxygen, and hypoxemia is less oxygen in blood. The fact is that almost all of us may and often do experience hypoxia at some time during our daily lives even though we don’t realise it. There are periods of hypoxemia in the pathogenesis of most chronic diseases, especially in the severe forms of the diseases (COPD, bronchial asthma, sleep apnoea, sudden infant’s death syndrome (SIDS), cystic fibrosis, heart failure, diabetes, severe anaemia, etc.). So hypoxemia may be destructive if it is severe and if it lasts a long period of time (days or months). The destructive effects of hypoxemia are:
- myocardial hypertrophy (especially of the right ventricle);
- cell damage, etc.
But brief periods of hypoxemia (the same as during the usual IHT session) result in adaptation to hypoxia without destructive effects. The IHT effects are non-specific as the effects of exercise training, during which there are also mild to moderate hypoxemia periods, especially in working muscles. So such hypoxemia is really physiological. Moreover, such adaptation creates some beneficial protective effects. The known examples of beneficial effects are:
- the increase of maximal expiratory airflow;
- the increase of lung diffusion capacity;
- the increase of the external breathing efficiency;
- the increase of the blood oxygen capacity (erythropoetin, haemoglobin);
- the increase of the antioxidant capacity in blood and tissues;
- the increase of the vascularisation in different organs (skin and myometrium for this current state);
- changes in the activity of the transcription factors (NF-kB, AP1 and Sp1) in the heart and the brain;

Charles Houston, the world known authority in high altitude medicine, suggests that adaptation to hypoxia is a classical example of Selye's General Adaptation Syndrome [1]. Hypoxia stimulates prompt alarm responses and resistance - "struggle" responses. The struggle responses are:
- increased lung ventilation (rate and depth of breathing);
- increased heart rate and output;
- increased circulating red blood cells;
- decreased blood flow to nonessential parts and increased in the brain and the heart;
- enzymatic changes permitting some anaerobic work;

If hypoxia is not too severe, the body acclimatises by slowly replacing these “struggle” responses with those that are more sustainable [1].

There are some experimental and clinical studies demonstrating the improved efficiency of oxygen transport and utilisation. The increase of peak external airflow, lung diffusion capacity and external breathing efficiency after the IHT course result in the increase of partial pressure of oxygen (PaO2) and oxygen saturation (SaO2) in the arterial blood [2, 3]. The significant increase (45-50%) of the erythropoetin level in the blood serum was demonstrated after 5 IHT sessions [4]. EPO stimulates an increase in red blood cells and
haemoglobin formation, which is an important part of adaptation to hypoxia. Such changes in the oxygen transport system explain the possibilities to increase the exercise tolerance by IHT.

Significant is the increased capacity of various antioxidant systems in the organism and the decreased activity of main systems generating active oxygen species [5, 6].

In animal experiments IHT protects the brain of rats from oxidative stress induced by the neurotoxin 1-metil-4-phenyltetrahydropyridine (MPTP) and prevents development of corresponding behavioural disturbance [7].

The cardio protective effects of IHT have been demonstrated in both animals [8] and humans [9].

The IHT safety has been proven in placebo-controlled studies [2, 6, 10-13], however there exist counter-indications. Counter-indications to IHT include all acute somatic and infectious diseases; chronic diseases decompensation; pregnancy less than 16 weeks; pulmonary hypertension (clinical, ECG and/ or echocardiography signs); SaO2 at rest 92% and less; age 70 and over (the clinical study of IHT has not been carried out in this age group).

**IHT in Internal Diseases**

The results of studies including placebo controlled demonstrated good tolerance and no significant side effects in adults and children with mild and moderate bronchial asthma [10, 14, 15]. The IHT sessions did not result in a lengthy and substantial increase of pulmonary artery pressure and a decrease of peak forces expiratory flow. Nevertheless we consider IHT to be a counter indication for patients with severe bronchial asthma.

Published clinical investigations data suggest the beneficial changes in the bronchial asthma time course after the IHT course. It is suggested that beneficial effects in the course of bronchial asthma occur due to less incidents of respiratory infections and a decrease of bronchial hyperreactivity [14]. At present we analyse the results of a large-scale randomised study “IHT in children with recurrent bronchitis and bronchial asthma”. In the animal experiment on rats IHT has not resulted in the right ventricle
hypertrophy [16,17]. The effect of adaptation to interval hypoxia on ischemic and reperfusion arrhythmias has also been studied. The duration of ventricular tachycardia and ventricular fibrillation has decreased more than 2-fold during acute ischemia and more than 3.5-fold during reperfusion compared to control [16]. At the same time adaptation to hypoxia did not increase catalase and superoxide dismutase activity in the myocardium though significantly increased initial velocity of Ca transport in the sarcoplasmatic reticulum and increased its tolerance to induced lipid peroxidation and high Ca concentrations [18].

The experimental study performed in the Ottawa University [8] showed a large decrease in the nuclear content of the pro-inflammatory transcription factors (NF-kB, AP-1, Sp1) in the IHT hearts. The data suggest that IHT cardio protection may be caused by an increased anti-inflammatory capacity and decreased susceptibility to stress in preconditioned to hypoxia hearts.

In clinical study performed on patients with coronary heart disease and stable angina [9] the IHT individual regimens were safe even in the patients with severe functional classes of angina. No significant myocardial ischemia (clinical ECG and Echo-cardiographic data) and cardiac arrhythmia were caused by IHT in the patients with 1st and 2nd functional classes of angina. IHT safety in aged patients with CHD was proved in the recent placebo controlled study in the University of Innsbruck (in press). The improvement of exercise tolerance after IHT in the patients with stable angina is the most important result of the first study (the average exercise threshold growth was 24 Watts). At the same time the double product (heart rate multiply systolic blood pressure) significantly decreased at sub threshold loads [9]. The same double product decrease at sub maximal exercise after IHT was observed in the placebo controlled study in healthy students of the University of Innsbruck [11].

Some investigations studied the effect of IHT on the levels of lipids in persons with primary hypercholesterolemia [19]. After the IHT course the total cholesterol level significantly decreased due to a decrease of low-density cholesterol. The authors suggest that such IHT influence on lipid metabolism is caused by enhanced cholesterol hydroxylation in hepatocytes (considerable 30%-40% increase of primary bile acids concentration and no changes in ether cholesterol spectre were observed). Mention should be made that there was no comparable control in this study. In our opinion IHT can be a part of a rehabilitation program of patients with stable
forms of coronary heart disease instead of/ or combined with exercise training, especially in patients with subjective or objective counter indications to exercise training.

Studying the possible effects of IHT in females with coronary heart disease combined with climacteric syndrome when substitution hormonal therapy is counter indicative is promising. The increase of ovarian hormone production was demonstrated in placebo controlled study in perimenopausal women with hypoestrogenemia [20].

Unexpected results were obtained in the pilot study of IHT in the patients with non-insulin-dependent diabetes mellitus [3] (tissue hypoxia plays an important role in pathogenesis of this disease). The IHT course in the patients with compensated and sub compensated diabetes did not result in the increase of tissue hypoxia, the lactate and pyruvate blood serum levels were used to evaluate the degree of tissue hypoxia. Moreover, in sub compensated patients the lactate and pyruvate levels significantly decreased after IHT. According to the data of vibration and taste sensitivity investigations these biochemical changes were combined with less distal sensory polyneuropathy expression [21]. Today we can ascertain that non-insulin-dependent diabetes mellitus is not a counter indication for IHT.

Similar can be suggested in terms of patients with rheumatoid arthritis. The IHT safety in the patients with rheumatoid arthritis was proved in preliminary pilot studies. IHT did not cause the changes of the disease time course though patients noted a certain antianginal effect and a 2-fold reduction in the morning stiffness duration [22,23].

**IHT in surgery:**

*preparation of patients for surgery and anaesthesia*

The placebo-controlled study [24] carried out in pregnant women of a high risk group before the planned abdominal delivery showed a decrease both in pre- and post-operation stress-reaction. IHT prevented the rise of epinephrine (the epinephrine level had been lower 40% before the operation and 25% after the operation in the
IHT group compared to placebo), and the glucose level in blood before and immediately after the operation as well as oxidative stress induced by excessive generation of active oxygen species [6].

IHT produced the increase of the erythropoietin level (6.5-3.9 mU/ml before the IHT course and 10.1-1.5 mU/ml after 15 IHT sessions) [4] and of haemoglobin (5%-15%) (6,25) in blood preventing the development of post-operation anaemia. IHT increased the filtration of whole blood as well as erythrocytes [25].

Women who underwent a course of IHT prior to the planned abdominal delivery [26] or to uterine myoma surgery [27] displayed an increase (35%-40%) in relative volume of myometrium vasculature accompanied by a decrease in stroma volume. In placebo-controlled studies carried out in apparently healthy persons [12] and patients with climacteric syndrome [13] IHT improved their psycho emotional status (the decrease in mental strain and autonomic disorders). In the patients operated on for uterine myoma, wound healing was improved [28]. Each IHT session also means the training of respiratory muscles. The IHT course was noted to increase peak forced expiratory flow and the lung diffusion capacity [9, 29, 30], which brings the possibility to use IHT in the pre-operative period in patients with mild and moderate bronchial asthma and chronic bronchitis without respiratory insufficiency. The studies carried out in volunteer athletes [11] and coronary heart disease patients with stable angina [9] noted that IHT significantly decreased heart rate, the double product and pulmonary ventilation at sub maximal exercise compared to placebo. Thus, IHT improves the reserves of the organism providing for the economical fulfilment of exercise.

We suggest that the most important indications for IHT in planned surgery are the cases of bronchial asthma, chronic bronchitis, and iron deficient anaemia.

Some mechanisms of Interval Hypoxic Training are still unknown but its beneficial effects are obvious.

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