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Optimization of Clinical Application of Interval Hypoxic Training

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To improve the efficiency and acceptability of the hypoxia training procedures, a new method of interval hypoxic–hyperoxic training (IHHT) is suggested. This method uses hyperoxic rather than normoxic intervals between hypoxic gas breathing sessions. During these periods, the patient inhales through a mask gas mixture containing 30-40% O_2. Switching between hypoxia and hyperoxia phases and adjustment of their durations is performed using the principle of biofeedback, which allows the individual patient's sensitivity to hypoxia to be taken into account. In pilot placebo-controlled clinical trials, the efficiency (improved exercise tolerance, hypoxic resistance, normalization of lipid status), safety, and tolerability of individually adjusted IHHT were demonstrated.

Interval hypoxic training (IHT) or hypoxytherapy is a method for non-drug therapy and prophylaxis of noninfectious diseases and aerobic training based on respiration of oxygen-deficient gas mixtures.

According to the conventional view, acute or chronic hypoxia causes pathology or progress of various diseases (cardiovascular, bronchopulmonary pathology, obesity, etc.) [1, 2]. It was shown clinically that short-term (5-7 min) hypoxic episodes with normoxic intervals activate adaptation reactions and increase human body tolerance to various pathologies. As in the case of high-altitude acclimatization, IHT activates hematological and non-hematological mechanisms (angiogenesis, glycolysis, lipolysis, etc.) [3, 4].

For more than 30 years, IHT has been used in clinical, rehabilitation, and sports medicine [1-3, 5, 6]. IHT apparatuses are available from many domestic and foreign manufacturers. They include pressure chambers, hypoxicators, and rebreathers available from Bio Nova, Climbi, Hypoxia Medical Academy, Metax (Russia), Biomedtech (Australia), HYPOXICO Altitude Training Machines (USA), Colorado Altitude Training (USA), etc.

Clinically significant effect of IHT is observed after 15-20 sessions and remains for 1-3 months. The efficacy of IHT depends on the individual sensitivity of the patient to hypoxia, stage of disease, and state of health [4, 5]. Efficacy of IHT can be increased using special training procedures [4]. The dose approach to hypoxia (combination of hypercapnic and hyperoxic respiratory gas mixtures) has been reported in [3, 7].

The IHT procedures are usually cyclic. The respiratory mask is applied for 5-7 min. Hypoxic gas mixture (HGM) is used. After 3-5 min of reoxygenation, the patient is allowed to breathe atmospheric air. A single procedure contains 4-8 cycles of variable duration. The degree of hypoxia is controlled using pulsoximetry. HGM with oxygen content 14-11% O_2 is used.

An urgent task is to increase IHT efficacy, thus reducing the duration of therapy. Increase in the number of procedures above 25 reduces the efficacy of IHT (O_2 concentration decrease below 10-11% is poorly tolerated by patients) and leads to side effects.

In our experiments, the IHT efficacy was increased using hyperoxic rather than normoxic intervals between hypoxic gas breathing sessions. During these periods, the patient inhales through a mask gas a mixture containing 30-40% O_2. Switching between hypoxic and hyperoxic phases and adjustment of their durations are performed using the principle of biofeedback, which allows the individual patient's sensitivity to hypoxia to be taken into account.

It is well known that generation of reactive oxygen species (ROS) is a typical reaction of the human body to hypoxia. ROS induces transcription of regulatory factors, antioxidation protection, anti-inflammation, oxygen utilization in mitochondria, etc. [8]. ROS in IHT is induced during reoxygenation. The same is typical of oxygenotherapy. Therefore, the combination of hypoxic and hyperoxic rather than normoxic sessions increases the ROS signal. It was demonstrated in pilot experiments

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that such mode of therapy has higher membrane stabilizing effect and increases stress and hypoxia tolerance of the heart and brain [8, 11].

The essence of the method is an individual approach to the duration of a hypoxic (or hyperoxic) session. The oxygen saturation (SaO_2) value is compared to the minimal individual level monitored in a preliminary hypoxic test (HT). If the individual SaO_2 minimum (±2%) is reached, the hyperoxic session is started with a 1-min delay. When the initial level of SaO_2 is reached, HGM is applied again.

An individual procedure is dosed as follows. HT is monitored for 10 min using a special mask and HGM with oxygen content 12%. Initial and minimal SaO_2 levels and time intervals (min) necessary to reach these values are monitored. The resulting values are transferred to a computer. The initial HGM used for hypoxytherapy contains 12% O_2; SaO_2 is monitored. When the minimal SaO_2 level is reached, a timer is switched on, and after 1 min the hyperoxic mixture is applied. The recovery phase continues until SaO_2 level reaches 95-98% of the initial value. After that, HGM is applied again.

Five or six procedures are followed by HT (12% O_2). If SaO_2 level is reduced to 10%, HT is repeated with 10% O_2. Ten hypoxytherapy procedures using 10% HGM are performed, while the total hypoxytherapy course includes 15 procedures given 5 times per week.

This method of hypoxytherapy was given the name interval hypoxic–hyperoxic training (IHHT). An apparatus for IHHT was developed (Fig. 1) [9, 10]. The ReOxy apparatus is available from AI Mediq S.A. (Luxemburg). The operation of the apparatus is based on the principle of biofeedback, which allows the individual patient's sensitivity to hypoxia to be taken into account. NaX and CaX are used as sorbents.

The operation of the apparatus is automated. To start the procedure, the initial SaO_2 level should be specified. The training is autonomous.

The pilot model of the apparatus for hypoxic–hyperoxic training contains a pressure source (compressor) and a sensor of gas consumption connected to a two-way gas separation device. The gas separation device is connected to the system via a valve and vacuum pump.

The structural diagram of the pilot apparatus for IHHT is shown in Fig. 2. The gas separation device contains a short-cycle adsorption unit comprising adsorbers 8 and 9, pneumatic valves 4 and 5, pneumatic valves 6 and 7, back valves 12 and 13, and rectifier 27. Compressor 2 is connected to adsorbers 8 and 9 of the short-cycle adsorption unit via accumulative receiver 3 and pneumatic valves 4 and 5; adsorbers 8 and 9 are separated by pneumatic valves 6 and 7. The adsorber output is connected to

Fig. 1. General view of the ReOxy apparatus.

back valves 12 and 13 to provide oxygen supply of accumulative receiver 14; it is also connected to pneumatic valves 10 and 11. Pressure regulator 15, run-off regulator 16, and run-off indicator 17 are connected to the receiver. Pneumatic valves 6 and 7 are connected to the vacuum pump. The gas mixture from the vacuum pump is applied to the accumulative receiver. Receiver 19 is connected to the run-off regulator 20 and run-off indicator 21. The compressor 2 and vacuum pump 18 are arranged as an integral unit activated with a common motor. A ventilator is placed near the motor, compressor, and vacuum pump. The ventilator supplies air to the output filter 1 of the compressor. Control unit 26 controls valves 4-7, 10, and 11. The control unit contains a timer, threshold unit, and regulation device. The timer synchronizes valves 4-7, 10, and 11. The threshold unit detects signals from pressure sensors 22 and 23, which are regulated by the timer. The threshold unit is adapted to gas concentration. The control unit adapts the timer signal to control valves 4-7, 10, and 11.

Consumption regulators 16 and 20 balance the gas mixture consumption. Oxygen concentration in hypo- and hyperoxic gas mixtures is regulated by varying time intervals T1 and T3, as well as the threshold of pressure sensors 22 and 23. Safety valve 28 is intended to reduce gas pressure at receiver 14 if it increases beyond 0.2 MPa.

The efficiency of the apparatus for generation of hypo- and hyperoxic gas mixtures is 25 liter/min or higher; oxygen concentration in hypoxic gas mixture, 10-14%; in hyperoxic gas mixture, 30-40%. The following parameters are monitored: HR (heart rate) (25-240 ± 3%), SaO_2 (70-100 ± 2%), output pressure (<2 kPa), noise (<50 dB).

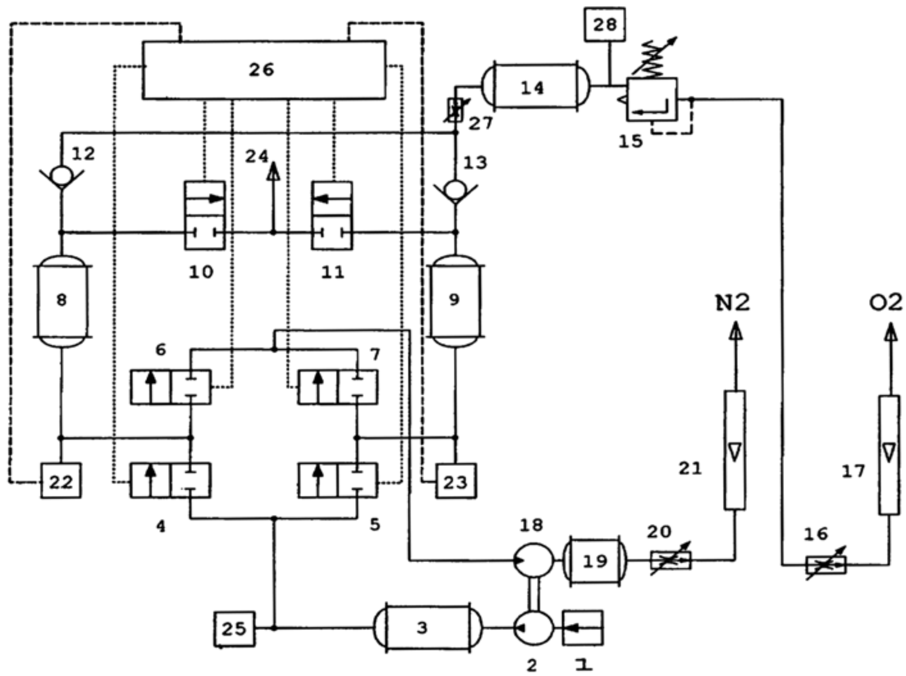

Fig. 2. Structural diagram of pilot apparatus for interval hypoxic–hyperoxic training.

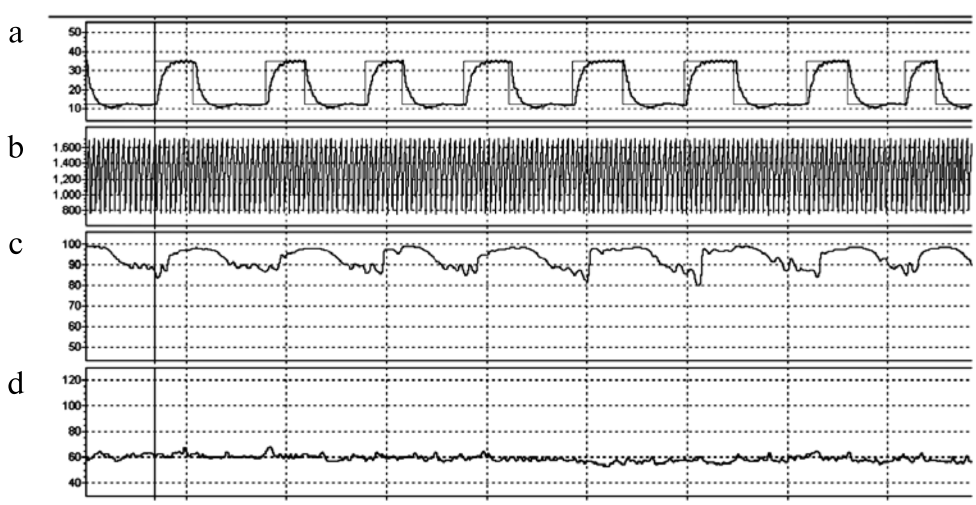

Fig. 3. IHHT procedure protocol in patient M.: a) O_2 concentration dynamics (%) in gas mixture; b) compressor pressure (kPa); c) SaO_2 (%); d) HR (beat/min); the vertical cursor indicates preset individual minimal SaO_2 value (80 ± 2%); when this value is reached, HGM is replaced with hyperoxic gas mixture (30% O_2) (Fig. 3, top curve).

The safety and efficiency of the IHHT method with feedback control of the gas supply were demonstrated in placebo-controlled tests [11-13] (see Fig. 3). The IHHT therapy of 35 patients with metabolic syndrome reduced body weight by 2.5-3.5 kg per month. The autonomous nervous system and biochemical status were also normalized. Impedance measurement demonstrated a decrease in the relative fat content. The content of cholesterol ($p <$

0.001), triglycerides ($p < 0.001$), and low-density lipoproteins ($p < 0.0001$) was confidently decreased [12].

The training effects of IHHT (stabilization of diastolic pressure) resulted in an increase in tolerance to hypoxia. Repeating the hypoxic test increased HR to HR_{max} and decreased SaO_2 to $SaO_{2\ min}$. The physical endurance of the patient increased. A 6-min walking test (6-MWT) demonstrated an increase in the ability to cover long distances.

In a group of 40 patients with chronic coronary heart disease (CCHD), 1 month after 20 IHHT sessions there was a significant increase in exercise tolerance (34.1% versus 2.7% in control) [11]. In the first test, symptoms of angina were observed in 11 patients, whereas after the repeat treadmill test the symptoms were observed in only 5 patients (4 patients in control both before and after tests). An increase in the aerobic capacity of patients with CCHD was accompanied by a decrease in body weight; normalization of lipid profile, AP, and HR; as well as improvement in hypoxic stability. The patients also reported a decrease in the number of ischemic attacks and anhelation severity [13].

The data on IHHT tolerance are very important. Side effects (anhelation, increased HR, vertigo) were observed in individual cases. However, in case of conventional IHT the side effects are known to be more frequent [4].

Conclusion

The method of interval hypoxic–hyperoxic training (IHHT) with feedback regulation of gas mixture supply suggested in this work increases the efficacy of hypoxic training. The introduction of this method provides promise for progress in non-drug therapy, rehabilitation, and prophylaxis. The IHHT procedure is easily tolerated and causes no side effects or complications. Normoxia–hyperoxia transition intensifies the training process, thereby increasing the hypoxic dose against the background of fewer procedures. The efficacy of the method of short alternating hypoxic–hyperoxic intervals is due to an increased range of variation of oxygen concentration in hypoxic and hyperoxic gas mixtures. The pilot model of the apparatus implementing this method proved to be reliable and effective. An increase in the cardiorespiratory endurance and medical rehabilitation of patients and sportsmen is an additional advantage of this method and the apparatus based on it.

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