When intermittent hypoxia can be useful

How to choose the optimal hypoxic exposure required to obtain therapeutic effects.

The efficacy of IH is dependent upon five key variables (Törpel et al.2019):

- the intensity of hypoxia
- the duration of hypoxia
- the number of cycles
- the pattern of IH presentation (e.g., consecutive days vs. alternating days)
- the total protocol duration

Only the controlled and dosed exposure to normo-baric hypoxia may be used as a therapeutic method.

Interval fasting and interval hypoxic training for activation of adaptive reserves of the body, prevention and treatment of degenerative brain diseases.

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Degenerative brain diseases (DGGM) and other cognitive dysfunctions can result from depletion of adaptive reserves in the brain as a result of aging, stress, depression, and inflammation. This leads to a violation of the correct signaling in the brain, between the brain and the body, as well as at the levels of organs, cells and molecules.
Fundamental concept: optimal health is activated and stimulated by intermittent stimuli - mild stressors (1, 2). We offer practical programs that combine two drug-free natural training / therapies, activation methods to increase the adaptive reserve of the human body: interval fasting (IG) and interval hypoxic training (IHT).
IG is a diet that consists in periodically refusing food with special preliminary preparation and getting out of hunger, sometimes with the intake of certain vitamins, minerals and electrolytes. The most frequent mode of interval fasting in our practice is a 2-3-5-day fasting regimen, repeated 3-2-1 times a month.
IHT is a way to increase the nonspecific resistance of an organism by adapting to hypoxia. Adaptation develops when breathing a hypoxic gas mixture (oxygen 10-13% and nitrogen about 87-90%), through a mask (at normal atmospheric pressure) in intermittent breathing for 3-5 minutes with an interval of 3-5 minutes, 6-9 cycles, session duration 40 - 90 minutes. To achieve the therapeutic effect of IHT, it is necessary within one session to provide a repeated, multiple (6-9 times) decrease in blood oxygen saturation (SpO2) from 94-99% to 80-88%.
The main measures for the prevention and rehabilitation of aging degenerative diseases should be to support the effectiveness of mitochondria, mitochondrial biogenesis and reduce the formation of improperly folded proteins in cells.
Mitochondria do not work efficiently and generate more superoxide when they are delivered and they consume large amounts of glucose and oxygen.
Our goal is to maintain the maximum efficiency of mitochondrial function, which can be achieved by delivering a varying amount of oxygen and glucose (a fairly low amount and normal), which is carried out in the process of IG and IHT. Combining these two methods of

periodic stimulation, we can synchronize brain functions faster and more efficiently and increase the brain's ability to plasticity and self-healing.
IHT can affect the key pathogenic factors of DGGM, such as excitotoxicity, Ca2 + homeostasis disturbances, oxidative stress, impaired synthesis of nitric oxide (NO) and impaired cerebral circulation.

The protective mechanisms of adaptation to hypoxia can be associated with a limitation of oxidative stress in the hippocampus, a limitation of the decrease in NO formation caused by b-amyloid, and an increase in the density of the vascular network in the brain (3).
IG stimulates the emergence of three main protective and therapeutic benefits for the brain: increased autophagy (4), increased levels of cerebral neurotrophic factor (BDNF) (5), and ketosis (2). Ketone bodies, such as hydroxyl butyrate, are neuroprotective.
IG can protect neurons from oxidative and metabolic stress in animal models of Parkinson's disease (5), Alzheimer's disease (6), and stroke (7). The activity of cytokines as a result of IG has a neuroprotective effect. Leptin and adiponectin levels also mediate neuroprotective effects. The sirtuin gene family (sirtiun) and the corresponding proteins that arise as a result of IG have a wide range of effects that improve health and longevity (9, 10).
To ensure maximum positive results, it is important to choose an individual program of IHT and IG with a truly therapeutic food regimen that reduces stress of the endoplasmic reticulum.

Fasting helps trigger a more gentle expenditure of energy by the cell, as it leads to the activation of an AMP-dependent kinase - AMPK. As a result of the activation of AMPK, the processes of maintaining a sufficient number of stem cells in tissues are activated, neoplasms are inhibited. Restorative nutrition is an important stage in treatment. It is possible to achieve a significant reduction in stress of the endoplasmic reticulum, to increase the antitoxic protection of the cell, to suppress inflammation by connecting certain food products activating Nrf2, and the transcription factor PGC-1a, which helps to restore mitochondria.
It is important to harmonize the programs of both methods to ensure maximum and long lasting results. The duration, frequency of respiration cycles and the amount of oxygen (which determines the strength of episodes / cycles of hypoxia), on the one hand, and the duration of fasting with a regime of restorative nutrition are critical factors.
In our presentation, we present data from 30 years of experience in the use of therapeutic fasting in hospital and outpatient working conditions, as well as 25 years of experience in using IHT. These results support the idea that the selected programs are ideally combined for the treatment and prevention of DZGM. In our opinion, this strategy has a clear scientific approach and provides a practical breakthrough in the clinical management of chronic diseases.

Key words: interval fasting, interval hypoxic training, neuroprotective effects, degenerative diseases of the brain.

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ИНТЕРВАЛЬНОЕ ГОЛОДАНИЕ И ИНТЕРВАЛЬНАЯ ГИПОКСИЧЕСКАЯ ТРЕНИРОВКА ДЛЯ АКТИВАЦИИ АДАПТИВНЫХ РЕЗЕРВОВ ОРГАНИЗМА, ПРОФИЛАКТИКИ И ЛЕЧЕНИЯ ДЕГЕНЕРАТИВНЫХ БОЛЕЗНЕЙ МОЗГА.

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Дегенеративные заболевания головного мозга (ДЗГМ) и другие когнитивные дисфункции могут быть результатом истощения адаптивных резервов в головном мозге в результате старения, стрессов, депрессии и воспалений. Это приводит к нарушению корректной сигнализации в мозге, между мозгом и телом, а также на уровнях органов, клеток и молекул.

Фундаментальная концепция: оптимальное здоровье активируется и стимулируется прерывистыми стимулами - мягкими стрессорами (1, 2). Мы предлагаем практические программы, сочетающие две без медикаментозной натуральной тренировки / терапии, методы активации для повышения адаптивного резерва организма человека: интервальное голодание (ИГ) и интервальную гипоксическую тренировку (ИГТ).

ИГ - это режим питания, заключающийся в периодическом отказе от еды со специальной предварительной подготовкой и выходом из голода, иногда с приёмом некоторых витаминов, микроэлементов и электролитов. Наиболее частым режимом интервального голодания в нашей практике является режим 2-3-5-ти дневного голодания повторяющееся 3-2-1 раз в месяц.

ИГТ - способ повышения неспецифической резистентности организма за счет адаптации к гипоксии. Адаптация развивается при дыхании гипоксической газовой смесью (кислорода 10-13% и азота около 87-90%), через маску (при нормальном атмосферном давлении) в прерывистом режиме: дыхание в течении 4-5 минут гипоксической газовой смесью с перерывом 4-3 минут (дыхание воздухом комнаты - уровень моря), то есть 4/4 или 5/3, 6-7 ***циклов***, длительность сеанса 40 - 55 минут. Для достижения лечебного эффекта ИГТ необходимо в течении одного сеанса обеспечить повторяемое, многократное (5-7 раз) снижение насыщения крови кислородом, снижение сатурации кислорода (SpO_2) с 94-99% до 80-88%.

Основными мерами профилактики и реабилитации стареющих дегенеративных заболеваний должны быть поддержка эффективности митохондрий, биогенеза митохондрий и уменьшение образования неправильно свёрнутых белков в клетках.
Митохондрии не работают эффективно и генерируют больше супероксида, когда им доставляется и они потребляют большое количество глюкозы и кислорода.
Наша цель - поддерживать максимальную эффективность функции митохондрий, что может быть достигнуто путем доставки меняющегося количества кислорода и глюкозы (достаточно низкого количества и нормального), что осуществляется в процессе ИГ и ИГТ. Объединяя эти два метода периодической стимуляции, мы можем быстрее и эффективнее синхронизировать функции мозга и увеличить способность мозга к пластичности и самовосстановлению.

ИГТ может влиять на ключ патогенных факторов ДЗГМ, таких как: эксито-токсичность, нарушения гомеостаза Ca2 +, окислительный стресс, нарушенный синтез оксида азота (NO) и нарушение мозгового кровообращения.

Защитные механизмы адаптации к гипоксии могут быть связаны с ограничением окислительного стресса в гиппокампе, ограничением снижения образования NO, вызванным b-амилоидом, и увеличением плотности сосудистой сети в головном мозге (3).

ИГ стимулирует возникновение **трёх основных защитных и терапевтических преимуществ для мозга**: увеличение аутофагии (4), увеличение уровня мозгового нейротрофического фактора (BDNF) (5) и кетоз (2). Кетоновые тела, такие как гидрокс бутират, являются нейро-протекторами.

ИГ может защитить нейроны от окислительного и метаболического стресса на животных моделях болезни Паркинсона (5), болезнь Альцгеймера (6) и инсульта (7). Активность цитокинов в результате ИГ оказывает нейро-протективное действие. Уровни лептина и адипонектина также опосредуют нейропротекторные эффекты. Семейство сиртуин генов (sirtiun) и соответствующие белки, которые появляются в результате ИГ, обладают широким спектром эффектов, улучшающих здоровье и долголетие (9, 10).

Для обеспечения максимальных положительных результатов важно подобрать индивидуальную программу ИГТ и ИГ с реально лечебным пищевым режимом, уменьшающим стресс эндоплазматической сети.

Голодание способствует запусканию более бережного расходование клеткой энергии, так как приводит к активации АМФ-зависимой киназы - АМФК. В результате активации АМФК активируются процессы поддержания достаточного количества стволовых клеток в тканях, тормозятся новообразования. Восстановительное питание - важный этап в лечении. Можно добиться значительного уменьшения стресса эндоплазматической сети, повысить противотоксическую защиту клетки, подавить воспаление с подключением определенных продуктов питания активирующих Nrf2, и фактора транскрипции PGC-1a способствующим восстановлению митохондрий.

Важно согласовать программы обоих методов, чтобы обеспечить максимальный и продолжительный результат. Длительность, частота циклов дыхания и количество кислорода (определяющее силу эпизодов/циклов гипоксии), с одной стороны, и длительность голодания с режимом восстановительного питания являются критическими факторами.

В нашей презентации мы представляем данные 30-летнего опыта использования лечебного голодания в госпитальных и амбулаторных условиях работы применения, а также 25-ти летний опыт использования ИГТ. Данные результаты поддерживают идею о том, что выбранные программы идеально сочетаются для лечения и профилактики ДЗГМ. По нашему мнению, эта стратегия может обеспечить практический прорыв в клинической помощи и научном подходе к этим заболеваниям.

Ключевые слова: интервальное голодание, интервальная гипоксическая тренировка, нейропротекторные эффекты, дегенеративные заболевания головного мозга.

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Intermittent hypoxic training as an effective method of activation therapy.

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Abstract
This article considers the possibilities of achieving the most effective therapeutic effect of intermittent hypoxia training (IHT) by initiating an activation and training reaction. Thanks to IHT the body builds an anti-stress type adaptation which increases the body's non-specific

resistance to the development of diseases. It works through a variable functional load which includes a mechanism for optimizing mitochondrial respiration and is a trigger for synchronizing the working of the nervous, immune and hormonal systems. It is used to great effect in the training of astronauts, pilots, athletes and in the treatment of diabetes mellitus, trophic ulcers, diseases of the cardiovascular system, the central nervous system and oncological disorders. In addition, laboratory and hardware methods of diagnosing for the selection of individual IHT regimes are proposed. Some biochemical data presented in the article demonstrate the effects of moderate hypoxia. These data apparently constitute an integral effect of activation and training reactions. The efficacy and diversity of the therapeutic and preventive action of IHT makes it possible to recommend it for the training and rehabilitation of athletes and the treatment and rehabilitation of both in- and out-patients.

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Intermittent Fasting and Intermittent Hypoxia Training against degenerative brain diseases.

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Aesthetic Dermatology and Surgery, Preventive and Anti-Aging Medicine

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Degenerative brain diseases (DBD) and other cognitive dysfunctions may result from an exhaustion of adaptive reserves in the brain by aging, stress, depression and inflammation. These lead to destruction of signalling within brain, between brain and body, organs, cells and molecules. The fundamental concept: optimal health is promoted by intermittent challenges (mild stressors). Cells in the organ, in this case the brain, respond adaptively by enhancing their ability to function and resist disease. It appears that stimulation of the self-defence systems in neural cells is a promising strategy in restricting the progression of DBD.

We offer practical programs combining two non-drug environmental activation methods for the adaptive reserve: Intermittent Fasting and Intermittent Hypoxia Training. The main actions of preventive and rehabilitation of aging degenerative diseases should be to support the effectiveness of mitochondria, mitochondria biogenesis and reduce the cellular effects of protein misfolding. Mitochondria do not work efficiently and generate more superoxide if there is a higher-energy intake e.g. high and excessive supply of glucose and oxygen. Our approach combines Intermittent Fasting (IF) and Intermittent Hypoxia Training (IHT), which can support the effectiveness of mitochondria and synchronise signalling functions of the whole body and the brain. IHT could influence the key of pathogenic factors of DBD, such as: excitotoxicity, Ca2+ homeostasis disruptions, oxidative stress, disturbed synthesis of Nitric Oxide (NO), and impaired cerebral circulation.

The protective mechanisms of adaptation to hypoxia may be related to restriction of oxidative stress in the hippocampus, the limitation of a decrease in NO production induced by b-amyloid, and increased density of the vascular network in the brain. (Possible use of adaptation to hypoxia in Alzheimer's disease: a hypothesis. Igor Yu. Malyshev, at el. 2012).

IF can also increase neurotrophic factors signaling in brain cells, which may contribute to its abilities to enhance hippocampal neurogenesis (Lee et al., 2002) and protect neurons against oxidative and metabolic stress in animal models of Parkinson's disease (Duan and Mattson, 1999), Huntington's disease (Duan et al., 2003), Alzheimer's disease (Halagappa et al., 2007) and stroke (Yu and Mattson, 1999; Arumugam et al., 2010). IF has also been shown to have neuroprotective effects potentially capable of warding off Parkinson's and Alzheimer's. The cytokine activity as a result of this dietary pattern has neuroprotective effects. Leptin and adiponectin levels also mediate neuroprotective effects. The Sirtiun gene family and the corresponding proteins have a wide variety of health and longevity enhancing effects. (Nutrients 2010, 2(5), 551-571; Review. Emma De Fabiani at al.).

It is important to determine the details of both methods to ensure the maximum beneficial result. The duration, frequency, and severity of hypoxic or fasting episodes are critical factors. In our presentation we present the data of 38 years experience of fasting therapy in hospital and out-patients (at home), as well as 15 years using IHT, that support the idea that selectively chosen programs of these two methods could build adaptation and help with prevention of DBD. In our opinion this strategy may provide a break-through in the clinical approach to these diseases.

Key words: degenerative brain diseases, Integrated Therapy, Intermittent Hypoxia Training, Intermittent Fasting, activation of adaptive reserves, preventing aging diseases.

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Diabetes type 2 and cancer: an integrative approach to prevention and rehabilitation.

AMEC 2013
14-15 June 2013,
Moscow - Russia

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Background: People with diabetes type 2 (D2) are nonetheless more likely to develop cancer, so cancer should be numbered among the complications of diabetes and has some similar characteristics in pathogenesis. D2 and cancer are misfolded protein diseases. Lessening of endoplasmic reticulum (ER) leads to a reduction in misfolded proteins and a reduction of protein aggregate (toxic, non-functional, related to infections, p53 mutation protein). Preventive D2 leads to improving insulin receptors, decreasing glycation, balancing nitric oxide, reducing free radicals and coordinating cell signalling. The main actions of preventive and rehabilitation of cancer and D2 should be support the effectiveness of mitochondria and reduce the cellular effects of protein misfolding. Mitochondria do not work efficiently and generate more superoxide if there is a higher-energy intake e.g. high and excessive supply of glucose and oxygen. Our approach combines Intermittent Caloric Restriction (ICR) and Intermittent Hypoxia Therapy (IHT), which can synchronise body functions and support the effectiveness of mitochondria.

Patients, material, methods: To discover the effectiveness of the Integrated Therapy for D2 patients we aimed to evaluate changes in clinical conditions by comparing different ICR

regimes: complications, body weight dynamic, blood glucose, glucosuria, decreasing low-sugar tablets and insulin dosage or complete absence of both. 42 patients with D2 with some evidence of vascular complications and 20 diabetic control patients, who were treated in hospital in the usual way (diet, physiotherapy, hypoglycemic medicine), were included in the study.
The 42 patients were randomized into 3 groups, each with a different period of fasting over 24 hours and a last meal before 20.00: the first group of 22 patients had the usual hospital diabetic diet, regime N9, and fasted 12 hours overnight, beginning each day with a breakfast at 8.00. The treatment continued for 9-10 days (Moscow Hospital). The second group of 16 had 16 hours fasting with breakfast delayed until 12.00. Their treatment lasted 10-15 days. The third group of 4 fasted for 18 hours and had their first meal at 15.00. The second and the third group had the treatment at a private practice in London. All patients were given integrated IHT, low sugar tablets, if required, plus chromium (100µl per day) and acupuncture, which decreased their appetite.

Diabetes type 2 and cancer: an integrative approach to prevention, treatment and rehabilitation.

11th Anti-Aging Medicine World Congress
3 - 4 April 2013, Monaco

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Background: Diabetes type 2 (D2) and cancer are misfolded protein diseases. People with D2 are nonetheless more likely to develop cancer, so cancer should be numbered among the complications of diabetes. Lessening of endoplasmic reticulum (ER) is leading to a reduction in misfolded proteins and a reduction of protein aggregate (toxic, non-functional, related to infections, p53 mutation protein). This is achieved by improving insulin receptors, decreasing glycation, balancing nitric oxide, reducing free radicals and coordinating cell signaling. Mitochondria do not work efficiently and generate more superoxide if there is a higher-energy intake e.g. high and excessive supply of glucose and oxygen. Intermittent Caloric Restriction (ICR) and Intermittent Hypoxia Therapy (IHT) can synchronies body functions, support the effectiveness of mitochondria, decrease endoplasmic reticulum stress, prevent and reduce the cellular effects of protein misfiling.

Patients, material, methods: To discover the effectiveness of the Integrated Therapy for D2 patients we aimed to evaluate changes in clinical conditions by comparing different ICR regimes: complications, body weight dynamic, blood glucose, glucosuria, decreasing low-sugar tablets and insulin dosage or complete absence of both. 42 patients with type D2 with some evidence of vascular complications and 20 diabetic control patients, who were treated in hospital in the usual way (diet, physiotherapy, hypoglycemic medicine), were included in the study.
The 42 patients were randomized into 3 groups, each with a different period of fasting over 24 hours and a last meal before 20.00: the first group of 22 patients had the usual hospital

diabetic diet, regime N9, and fasted 12 hours overnight, beginning each day with a breakfast at 8.00. The treatment continued for 9-10 days (Moscow Hospital). The second group of 16 had 16 hours fasting with breakfast delayed until 12.00. Their treatment lasted 10-15 days. The third group of 4 fasted for 18 hours and had their first meal at 15.00. The second and the third group had the treatment at a private practice in London. All patients were given integrated IHT, low sugar tablets, if required, plus chromium (100µl per day) and acupuncture, which decreased their appetite.

Results: all the patients showed signs of increased energy and mood after 2-3 days of treatment, depression disappeared, lower doses of insulin and tablets were given. There were improvements in connection with angiopathy of extremities (the numbness and pain were gone); water retention and weight were reduced. The blood pressure improved. The most remarkable result was achieved with the patients from group 3, who had a longer period of day fasting. Patient 1 - 60 years old Vahan E. has been without D2 for the last 12 years; he had D2 for 6 years previously. Patient 2 - David M., 73 years old with a lung abscess received 25 sessions during the 27-day treatment. The abscess was cured during that period. Patient 3 - Joanne T., 60 years old, insulin reduction from 180 units to 36 within the 5 day treatment. She had been taking this dose of 35 units without an increase until the last observation in 2005. Patient 4 - Ron G., 62, D2 and psoriasis, received the treatment over 3 months in 2005; he lives without diabetes and psoriasis at present.

Conclusions: We demonstrated that D2 patients with IHT, with diet regime 9, ICR and acupuncture responded well and rapidly to the treatment in comparison with the control group. Symptoms of vascular complications and diabetic neuropathy showed improvement without additional medicine and physiotherapy, extremities felt warm and oedema, if present, was reduced. The quality of sleep, psychic status and motivation were improved on the second day of treatment. Comparing the three groups we observed the best result in the second and the third group. In group 3 three patients no longer required hypoglycemic medicine previously taken for 5-12 years. The cellular effects of protein misfolding provide a common framework that may contribute to guide preventive and treatment strategies of D2 and cancer as two ageing diseases.

Key words: Diabetes type 2, Cancer, Integrated Therapy, intermittent hypoxia therapy (IHT), Intermittent Caloric Restriction (ICR), acupuncture, preventing aging diseases.

Intermittent Hypoxic Therapy/Training (IHT) as Etiological and Pathogenetic Anti-Aging Treatment

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Oxidative mtDNA damage is a recognised pathogenic mechanism of aging in mammals. Progressive degradation of mitochondria underlies oxidative stress, which causes accumulative molecular damage, genomic instability, telomeres shortening, metabolic and hormonal decline, accelerate protein glycation and diminish protein turnover. Continuous rejuvenation of mitochondria in somatic cells can reduce oxidation stress, increase efficiency of oxidative metabolism, slow down aging process, prevent and/or retard development of age-related pathology.

A natural mechanism of mitophagy recently discovered in mammals facilitates continuous purification of the mitochondrial pool in an organism from the most ROS-producing mitochondria.

Mitophagy selectively eliminates them, thus providing advantage for proliferation of wild-type (non-mutated) mtDNA. Mitophagy can be induced by time – and pO2 tension-controlled cycling of intracellular pO2 from normoxic to hypoxic state and back in the range between 5 -1 torr. Such O2 oscillations can be safely induced by Intermittent Hypoxic Therapy/Training (IHT).

IHT is a novel preventative, therapeutic and rehabilitative treatment that has been developed and refined during the last decades. IHT improves autonomic homeostasis, modulates humoral and cellular immunity and markedly augments non-specific stress-resistance.
This brings measurable rejuvenation effects and rapid clinical improvements in numerous diseases, physical and mental conditions. The ability to regulate, adjust and balance metabolism via hypoxic preconditioning that modifies the cellular mitochondrial life cycle through HIF-1α (Hypoxic Induce Factor -1) and nitric oxide pathway is the most valuable property of IHT. The cellular and systemic effects of hypoxic preconditioning include: a) rejuvenation of mitochondria via mitophagy; a) decrease of reactive oxygen species generation; c) increased enzymatic and antioxidative defence; d) decreased lipid peroxidation; e) improved oxygen absorption, transportation and utilisation; f) improved glucose metabolism and enhanced accumulation of intracellular glycogen; n) increased accumulation of cytoglobins; h) increased erythropoietin and Hsp – 70 levels; i) facilitated mesenchymal stem cells-dependent tissue repair;) production of HIF-1α is the reason for containment of development of different types of cancer.

Technically, the IHT session consists of 6 -10 controlled repeated hypoxia-reoxygenation episodes: 3 - 6 minute intervals of hypoxic air inhalation (10 - 12% oxygen), interspersed with 3-5 minute intervals of normoxic (20.9% oxygen) air inhalation. Several times a week training for 2 - 4 weeks gradually induces beneficial clinical effects. The effects of IHT in healthy subjects are moderately expressed, while they are clearly noticed in patients, suffering from oxidation stress. To achieve better results from IHT the individualized protocols should be used, which based on the reaction (fluctuations) of Saturation Oxygen in blood (SpO2). The efficiency of IHT can be enhanced by intermittent caloric restriction, fasting for 2-3 days and by synergistic nutraceutical supplementation.

Results of the treatment of 102 patients are discussed. A detailed description and analysis of several clinical cases is provided.

Key words: Intermittent Hypoxic Therapy, mitochondria, HIF-1α, nitric oxide, ROS, mitophagy.

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Intermittent hypoxic training as an effective method of activation therapy.

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Abstract
This article considers the possibilities of achieving the most effective therapeutic effect of intermittent hypoxia training (IHT) by initiating an activation and training reaction. Thanks to IHT the body builds an anti-stress type adaptation which increases the body's non-specific resistance to the development of diseases. It works through a variable functional load which includes a mechanism for optimizing mitochondrial respiration and is a trigger for

synchronizing the working of the nervous, immune and hormonal systems. It is used to great effect in the training of astronauts, pilots, athletes and in the treatment of diabetes mellitus, trophic ulcers, diseases of the cardiovascular system, the central nervous system and oncological disorders. In addition, laboratory and hardware methods of diagnosing for the selection of individual IHT regimes are proposed. Some biochemical data presented in the article demonstrate the effects of moderate hypoxia. These data apparently constitute an integral effect of activation and training reactions. The efficacy and diversity of the therapeutic and preventive action of IHT makes it possible to recommend it for the training and rehabilitation of athletes and the treatment and rehabilitation of both in- and out-patients.

Introduction

Activation therapy is the impact on the human body of various biologically active factors, including adaptogens, physiotherapy or other stimuli to obtain a general non-specific reaction of the body that manifests itself in an increase in its viability. These effects have positive effects, directly or indirectly, through an increase in the effectiveness of tissue respiration.

At the present time, much experimental material has been accumulated on the beneficial effects of natural and experimental hypoxia on the human body. A special contribution to the study was made by N.A. Agadzhanyan (1,3,4,5); R.B. Strelkov and Chizhov A.Ya. (6,7,8,9,10); Volkov N.I. (11), A.Z. Kolchinskaya (12,13,14); S.G. Krivoshchekov (15,16) and many others. In recent years, controlled Intermittent Hypoxic Training (IHT) is widely used in clinical medicine. IHT is a method of increasing nonspecific resistance of the body via adaptation to hypoxia which lead to effectiveness of mitochondrial respiration.

Gas exchange is the fastest metabolism regulator. The oxygen we breathe is a natural stimulus, an activator that changes metabolism, expanding the range of adaptation. By changing the amount of oxygen in the gas composition, we directly affect mitochondrial breathing.

Reduction of oxygen tension in arterial blood and tissues acts as a reflex stimulus of receptive fields and nerve centers, which regulate physiological processes (17,18). In this case, the stimulus itself is habitual for the organism and, within certain limits, does not cause inadequate reactions. (19,20). That is why hypnotic training proved to be a successful tool for increasing the resistance of the human body to factors aviation and space flights (21,22,23).

Metod

In clinical conditions, hypoxic training with alternating breathing of ambient air is most often encountered with a mixture of 10-14% oxygen (O2) and about 86-90% nitrogen (N2) at normal atmospheric pressure (through a mask for 3-5 minutes), 6-9 cycles, with pauses between cycles of 3-5 minutes (respiration air at sea level, i.e. 20.9% O2). The duration of the session is 45 - 90 minutes. Adaptation develops as a result of breathing a hypoxic gas mixture, in a discontinuous mode, which lead to the repited shift of oxygen saturation in the blood (SpO2) from 100-94% to 86-78%. The oxygen content in the inhaled air varies from 10-14% (through the mask) to 20.9% (room air).

It is selected for each treatment the strength of the action of the hypoxic mixture (percentage of oxygen from 10% to 13%) hypoxic breathing cycle (3-5 minutes, respiration from 10% to 14% oxygen), breaks between cycles of exposure (3-5 minutes, respiration 20.9% oxygen) and the duration of the session (between 30 and 90 minutes).

Oxygen gives life, oxygen takes it. Without oxygen cells die. Too much oxygen - cells die even faster. Mitochondria determine a cell's choice between life and death. With a high energy consumption by the cell, i.e. with greater delivery of glucose and oxygen, the mitochondria do not work efficiently and generate more superoxide (O-2). Superoxide, as one of the active forms of oxygen under conditions of cellular stress, triggers and intensifies the sequence of reactions that ultimately lead to cell death. The metabolism of all eukaryotes is based on the reduction of oxygen to water (O2 to H2O). This reduction of O2 to H2O can occur only with the formation of reactive oxygen species (ROS). ROS - "signal for life" occurs in low concentrations of H2O2. Super oxide radical stimulates the division of normal cells of various tissues. On the other hand, H2O2 ROS and other ROS trigger the mechanism of cell death, the transformation of normal cells into malignant cells.

IHT, taking into account the doses in which we use it, can be called activation hypoxia, since it manifests itself as a physiological stimulus, and has many well-known beneficial effects.

What are the key biochemical changes which stimulate the entire body system into giving a general response to moderate hypoxic effects? In a state of hypoxia, the body tends to produce the required amount of energy from a smaller amount of available oxygen. This is the main generalized, summing effect of this method.

First, there is an immediate synthesis of Hypoxia Inducible Factor (HIF-1), which allows the cells to adapt to hypoxic conditions. HIF-1 activates many reactions aimed at improving the body's use of oxygen.

HIF-1, a transcription factor that increases the expression of vascular endothelial growth factor (VEGF) and VEGF receptors, alters the expression of genes controlling glucose transport and glycolysis, leads to an increase in the expression of erythropoietin (EPO) genes, glycolytic enzymes, such as aldolase A, Lactate dehydrogenase A gene, phosphofructokinase L gene, pyruvate kinase M gene. (24, 25). HIF-1a is synthesized in various tissues, including nervous tissue (26). It is found in all cells of the brain, but its expression in neurons is maximal.

The synthesis of HIF-1a leads to an increase in: Nitric oxide (NO), the synthesis of cytochrome-450, dopamine and serotonin, gamma-aminobutyric acid, thyroxine, insulin and improves the transport glucose. IHT increases the stress-protein (caperone, shock protein) level in the cell (27). There is an intensification of production and rejuvenation of mitochondria (a cell concentrator for the production of aerobic energy) and mitochondrial enzymes, which allows more efficient use of oxygen for energy production and excellent enzymatic antioxidant protection.

Oxidative damage to mitochondrial DNA, mtDNA, is a recognized mechanism of the pathogenesis of aging in mammals. Progressive degradation of mitochondria underlies oxidative stress, which leads to an accumulation of molecular damage, genome instability, reduction of telomeres, metabolic disturbances, hormonal disorders and acceleration of glycosylation of proteins. Continuous renewal of mitochondria in somatic cells can reduce oxidative stress, increase the efficiency of oxidative metabolism, slow the aging process and prevent and / or slow the development of age-related pathologies.

The natural mechanism of mitoptosis, recently discovered in the mammalian organism,

promotes the continuous purification of the mitochondrial basin in the body from damaged, old mitochondria. This actively produces free radical oxidation Reactive Oxygen Species (ROS). ROS include oxygen ions, free radicals and peroxides of both inorganic and organic origin.

Oscillations of oxygen delivery eliminate the destroyed mitochondria and stimulate mitoptosis, which is the key to longevity. (28) Mitoptosis facilitates purification of the mitochondrial basin thus ensuring the spread of unmutated mtDNA.

IHT improves blood circulation and oxygen delivery to tissues due to more efficient operation of the ATP-K + pump. It was discovered that the ATP-K channels of intact ventricular cardiomyocytes blocked by intracellular ATP in normoxic ambient conditions begin to open in the 20-25 minutes of moderate hypoxia. The dynamics of this activity has a periodic/cyclical rhythm. (29)

One of the most effective factors of the biochemical environment of the body is nitric oxide (NO). NO acts on the smooth muscle walls of the vessels relaxing them. Nitric oxide also promotes the inhibition of the proliferation of smooth muscle cells. There is decreased aggregation of platelets, leukocytes and erythrocytes; Reduction of adhesion of leukocytes to the endothelium. Nitric oxide induces neurogenesis and angiogenesis. Vascular growth occurs only where there is smooth musculature. This fact is important for solving the problem of the use of IHT in patients with cancer. As is known, the vessels of cancerous tumors do not have smooth muscle tissue lining them.

The synthesis of nitric oxide (NO) and its accessibility activates the expression of other protective factors, including: heat shock proteins (30) antioxidants, prostaglandins of H-synthase (31). IHT optimizes concentrations of nitric oxide by stimulating its synthesis, and also limiting its overproduction (32). Understanding the role of NO in the mechanisms of adaptation to hypoxia will help to substantiate the program for the prevention and treatment of hypoxia or ischemic damage to organs and cells and enhance the adaptive capacity of the organism.

What facilitates or hinders the realization of the biotropic effect of nitric oxide? Hyperglycemia inhibits the formation of nitric oxide (NO) and weakens its effect. IHT is more effective when it is used on the body in conditions of normoglycemia or in a state of hunger. During fasting there will be increased sensitivity of receptors. Even morning fasting can play a positive role. Adaptation to hypoxia prevents both NO overproduction and NO deficiency, resulting in an improvement in blood pressure (33). The lack of sufficient synthesis of NO in diabetes mellitus gives rise to a dysfunction of the endothelium, which in turn leads to vasospasm, smooth muscle proliferation, activation/ aggregation of platelets, adhesion of leukocytes to the endothelium (34).

IHT improves oxygen delivery to tissues due to a change in hemoglobin, an increase in tissue affinity for oxygen. During IHT, hemoglobin binds to 2,3-DPG (2,3-diphosphoglycerate), which greatly facilitates the release of oxygen from hemoglobin into the tissue (35).

The uniqueness of hypoxic stimulation is that during IHT there is an improvement in blood circulation in that part of the body that is in a state of hypoxia. Infected or inflamed tissue and organs become acidic, since they are in a state of hypoxia. During IHT, low pH of tissues and

organs stimulates capillary dilation faster than in non-acidified, healthy ones. Thus, blood circulation improves primarily in the affected tissues and organs.

That's why the uniqueness of IHT stimulation makes it possible to treat not only wounds, trophic ulcers, lung abscesses but also epilepsy, depression, Parkinson's and Altzheimer's diseases (32).

IHT as an activation method acts on the whole organism and undoubtedly has much more advantages in achieving a quick and lasting result in increasing the overall resistance of the organism than the methods of action of individual adaptogens. The impact of IHT immediately involves the brain changing its blood circulation and biochemical status. It is known that even ordinary anxiety changes the blood circulation and biochemical status of the brain in a mosaic and/or locally (36) and it may be enough to have one IHT session to delete it. Practice showed this.

Patients with such diseases as epilepsy, exacerbation of peptic ulcer, depression, anarexia and many others have in their brains their individual mosaic and / or local pattern, the dominant, with excessive accumulation of metabolites, altered (insufficient) tissue respiration and altered nervous excitability. Outstanding neurophysiologist Natalya Bekhtereva stressed that not changing the state of the brain can not cure the disease. IHT can help in this if it is used in parallel with traditional methods of treatment. Undoubtedly, the same mechanisms work in the prevention and treatment of the consequences of strokes and heart attacks.

The condition of the disease or a stable pathological condition, as Natalia Bekhtereva called it, is the "interconnected complex memory matrix" (37). The mechanisms of its "erasure" and "re-education" are the improvement of blood circulation, the "harvesting" of accumulated metabolites, the improvement of tissue respiration.

What studies confirm the antitumor effect of IHT on the body? IHT activates p53, a tumor suppressor. P53 (protein p53) - functions as a suppressor of the formation of malignant tumors, respectively, the gene TP53 is an anti-oncogene. Mutations of the gene TP53 are found in cells of about 50% of cancerous tumors. Often it is called the "guardian of the genome" (38). Hypoxia regulates telomerase (39).

IHT improves blood circulation in organs and tissues by relaxing smooth muscle in capillaries, but not in cancerous tumors. Cancer does not contain smooth muscles in the vessels, so there is no embolization of the capillaries or improvement in blood circulation in tumors. Also, VEGF does not cause proliferation of smooth muscle cells (as well as corneal endothelial cells, lens epithelial cells, fibroblasts and adrenal cortex cells) (40,41).

The methods of controlled (i e those methods which are under the control of the development of anti-stress reactions of training and activation) enhancement of adaptation or activation acting on the whole body undoubtedly have many more advantages in achieving a quick and lasting result than methods of uncontrolled, blind effect of individual adaptogens. In this respect, IHT exposure is precisely the controlled dose that is directed to the central neuroendocrine mechanisms of homeostasis regulation and immediately turns on the brain, changing its blood circulation and biochemical status. Even ordinary anxiety changes the blood circulation and biochemical processes of the brain in a mosaic and/or local fashion (42). Such diseases as epilepsy, exacerbation of peptic ulcer, depression, anorexia and many others have of course their own individual pattern of altered blood circulation and

biochemical state. The method of "re-education" with epilepsy with the help of electrostimulation (16) can be completely replaced by IHT.

The unique nature of hypoxic stimulation makes it possible to treat not only wounds, trophic ulcers, abscess of the lungs, but also epilepsy, depression, initial manifestations of Parkinson's and Altzeimer's disease. Undoubtedly, the same mechanisms of IHT work in the prevention and treatment of the consequences of strokes and heart attacks. The state of the disease or a stable pathological condition, as Natalya Bekhtereva pointed out, is "an interrelated complex memory matrix" (43). The mechanisms of its "erasure" and "re-education" are the improvement of blood circulation, the "harvesting" of accumulated metabolites and the improvement of tissue respiration.

What reactions can be observed in the patient's body immediately after IHT?
A positive response appears after 15-30 minutes, a state of general calm manifests itself, often accompanied by relaxation and drowsiness, a slowing down of breathing and heart rate. Some patients improve their color vision dramatically. Cheeks appear pink, limbs are warmed. After one - two sessions, sleep and mood improve. In some patients, long-term depression is cured. There is a comfortable feeling of relaxation in the stomach, "the lump in the throat or chest" often accompanies stress is gone. Digestion improves, increases the nonspecific resistance of the body as a result of integral changes in the body.

Breathing gas mixtures with different oxygen content causes hypoxia of different levels and leads to various reactions of the body. A weak stimulus causes a training reaction, which leads to the accumulation of substances (proteins, cells, tissues). A stronger stimulus is caused by the reaction of training and activation, which has temporary destructive properties, but in the further leads to a more intensive synthesis of proteins and repair. A very strong stimulus - causes stress, which leads to a noticeable destruction and hinders the development of an adaptive response.

Strong, intense hypoxia, like other strong stimuli, causes stressful reactions of anxiety, resistance and oppression within the 3 phases. Stressful reactions are accompanied by profound changes in the central nervous system, including the pituitary gland and its hypersecretion of ACTH, suppression of the activity of the thymic-lymphatic system, metabolic disorders and high energy expenditure. As the founder of stress Hans Selye said, "protecting the body from a strong stimulus is achieved at a high price - at the cost of breakage and high costs." Stress is the nonspecific basis of any pathological process.

IHT makes it possible to purposefully dose the stimuli, the fluctuations of the hypoxic mixture. The purpose of IHT is to cause the development of general nonspecific reactions, which correspond to the symptom complex of an integral nonspecific adaptation activation or training reaction described and studied by Rostov scientists. (44,45,46,47).
It is important to take into account the individual sensitivity and subjective sensations of the client (sleep, appetite, motor activity, efficiency, emotional state) and compare them with objective indicators. One of these can be a morphological blood test that classifies the strength of the impact and identifies the archetype of the reaction (training, activation, or stress) (48). Monitoring before and after a session heart rate variability (HRV) and study the thermography of the body, an electroencephalogram (EEG), indicates the dynamic of SpO2 and breath-holding time would be valuable.

Summary

Within nature, there are certain resources which can have a powerful and quick effect on the metabolism. They can kill or cure. Of these oxygen is among the strongest. Our aim is to design the most efficient IHT regime to act as a natural trainer, regulator and activator for restoration and rejuvenation for the body and brain.

Key words: intermittent hypoxia training, activation therapy, adaptation, sport performance, aging disease.

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