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The interval hypoxia in orthopedic practice

Introduction to the topic

Congenital and acquired diseases as well as injuries of the locomotor system are the domain of the orthopaedics (and accident surgery) department. The diagnostic and treatment methods in this field have been continuously developed and are still in a state of flux. In view of advancing medical-scientific knowledge, of the emergence of ever more innovative diagnostic (e.g. genetic tests) and treatment methods (e.g. PRP treatment or expanded possibilities of endoscopic spinal surgery), of the frequent rejection of surgical interventions by patients, of the "spoiling" of surgical procedures by cost bearers, media and studies of all quality levels as well as the market penetration of other providers of medical services (academic physiotherapists, osteopaths, chiropractors, etc.), the orthopaedist in private practice must ask himself again and again which specialist areas within the overall field of orthopaedics and trauma surgery he would like to perform and in which specialist areas he may have to develop further. Especially for orthopaedists in private practice and those with a conservative orientation, the general economic conditions in statutory health insurance medicine are so bad hence it becomes unavoidable to offer therapeutic options within the framework of private and self-paying medicine, which are effective, innovative and offer unique selling points compared to other providers and therapies..

One of these novel methods, which has great potential for treating selected orthopaedic patients, is Intermittent Hypoxia Hyperoxia Therapy, or IHHT for short. This is a conservative, non-invasive therapy in which different oxygen concentrations are applied as a physical stimulus in order to achieve a change in metabolism at the cellular level and an

increase in ATP energy production in the mitochondria. With the improved metabolic state and increased ATP production, the body is thus able to optimise repair mechanisms, better withstand physical stress situations, improve vegetative regulation and thus achieve pain reduction and a reduction in immune activation. IHHT is therefore not only a useful tool for orthopaedists, but can also be a useful therapy supplement in many other specialist areas.

Physiological basics of IHHT

The smallest structural unit of human life is the cell. Within this cell, the energy necessary for life processes is formed in the mitochondria. The citrate cycle and oxidative phosphorylation in particular form ATP molecules from the absorbed nutrients. While in the simple fermentation of glucose only 2 molecules of ATP can be formed from one molecule of glucose, the efficiency of energy production through the citrate cycle and oxidative phosphorylation increases up to 38 molecules of energy from one molecule of glucose (Löffler, 2012, p. 257). A disturbance of this energy production thus leads to relevant energetic deficits of the cells on the biochemical level, which are no longer able to carry out their original tasks sufficiently. This becomes relevant, for example, in the energy production of tumour cells (Warburg effect) (Kuklinski, 2016, p. 179, 307).

The system of cellular energy production can be severely disturbed by oxidative or nitrosative stress. The formation of oxygen radicals and/or peroxynitrite – caused by lack of cellular detoxification, sustained immune activation, toxic metabolites due to leaky-gut syndrome, disturbances of the system of basic regulation, etc. – promotes undesirable biochemical reactions, reduces membrane potentials and thus disrupts the proper functioning of cellular metabolism (Krebs, 2017 & Baker et al. 2005). The procedure of Intermittent Hypoxia Hyperoxia therapy with the alternating application of hypoxic and hyperoxic air begins at this point. Originating from the early phase of life on earth, the oxygen partial pressure of the environment has an important regulating influence on mitochondrial energy production (Löffler, 2012, p. 257).

This effect is known and still used today in the so-called altitude training of athletes, who not only stimulate the haemoglobin loading of erythrocytes but also the functioning of their mitochondria through training camps at higher altitudes (Friedmann, 2000, p. 418).

IHHT results from IHT, the intermittent application of hypoxic and normoxic air. Compared to the alternation of hypoxic and normoxic (room air) air, IHHT is more effective (Löffler, 2012, p.260). The hyperoxic phase (30 % oxygen) avoids possible undesired effects of hypoxia due to hyperstimulation (Bortfeldt, 2015). The additional hyperoxia phase also stimulates organ and cellular detoxification (Dünnenberger 2014-2017). Hypoxia (18-9% oxygen), in turn, prematurely eliminates ineffective mitochondria that do not produce sufficient ATP (apoptosis). At the same time, mitochondrial biogenesis, i.e. the formation of efficient mitochondria, is stimulated. The overall efficiency of mitochondria is increased. The antioxidative protective systems are also strengthened by the hypoxia phase. There is a change in the activity of the respiratory chain in the mitochondria without significant loss of ATP production. The resulting desired oxidative stress causes the aforementioned strengthening of the antioxidative protective systems (Bortfeldt, 2017). Hypoxia leads to an accumulation of the hypoxia inducible factor 1-alpha and the formation of erythropoietin and growth factors for angiogenesis (Wirth, 2009). This leads to a better supply of oxygen to the tissue. The body is better able to cope with short-term circulatory disturbances of the heart. By stimulating glycolysis enzymes and lactate dehydrogenase, hypoxia contributes to increased anaerobic ATP synthesis and faster lactate breakdown. The degradation of lactate prevents acidosis. Gene expression of insulin-dependent Glut 4 glucose transporters facilitates the process of glucose transfer into the cell. This effect has a positive effect especially on overweight people with metabolic syndrome (Chou, 2004). In addition, the body is supported in the long term in dealing with oxidative stress to avoid cell damage. The hypoxia sets an oxidative stress stimulus, whereupon the body reacts with an increased production of superoxide dismutase and glutathione peroxidase, the most important antioxidants of the body (Bortfeldt, 2015).

Practical implementation of IHHT

IHHT is a form of therapy that must be applied serially in order to be effective. Several treatment sessions of approx. 40 minutes each are necessary to achieve an effect. Experience has shown that patients unanimously report that at least ten sessions are necessary to achieve a lasting effect. 2 to 3 applications per week for optimal results. The therapy is carried out in a comfortable position while lying or sitting. Usually the patients fall asleep during the treatment.

During the first session, a hypoxia test should first be carried out, which is fully automated by modern systems such as MITOVIT®. The aim is to determine the initial oxygen concentration, which causes an oxygen saturation in the blood of less than 90 %. Only under this value a physiological effect of the IHHT can be expected. The first treatments are carried out with a gentle setting and a target value in the 89–85 % SpO2 range.

After 2–3 applications, the selected settings should be checked and the hypoxia phase should be adjusted. In order to achieve optimal treatment results, an SpO2 of 85–80 % should be aimed at after 2–3 applications.

A further fine tuning of the IHHT can be done via the ANS analysis, which should be performed initially and then every 3 to 5 sessions. The ANS analysis measures the vegetative regulation (integrated in MITOVIT®) during the IHHT treatment via the heart rate variability and thus controls

the stress stimulus of the hypoxia. The patient's subjective data, the heart rate and SpO2 parameters recorded by MITOVIT® as well as the real-time recording of the parasympathetic nervous system can be used to make precise fine-tuning.

In addition to manual adjustment of the oxygen quantity, MITOVIT® has a biofeedback program. This automatically adjusts the amount of oxygen so that the patient is in an optimal training range (see picture for the O2 range setting). The biofeedback program thus compensates for daily variations in the patient's reaction to hypoxia and, if necessary, provides more or less oxygen to achieve optimal therapy results.

If the oxygen saturation in the blood falls below the set safety value, more oxygen is automatically given again. The treatment can therefore be classified as very safe. The patient can therefore be left alone during the treatment.

Also innovative is the possibility of socalled adaptive hyperoxia. After the administration of hyperoxic air, the patient switches to normoxic air in order to enter the following hypoxic training phase more quickly and to optimise the hypoxia-induced training effects (see picture for the O2 range setting).

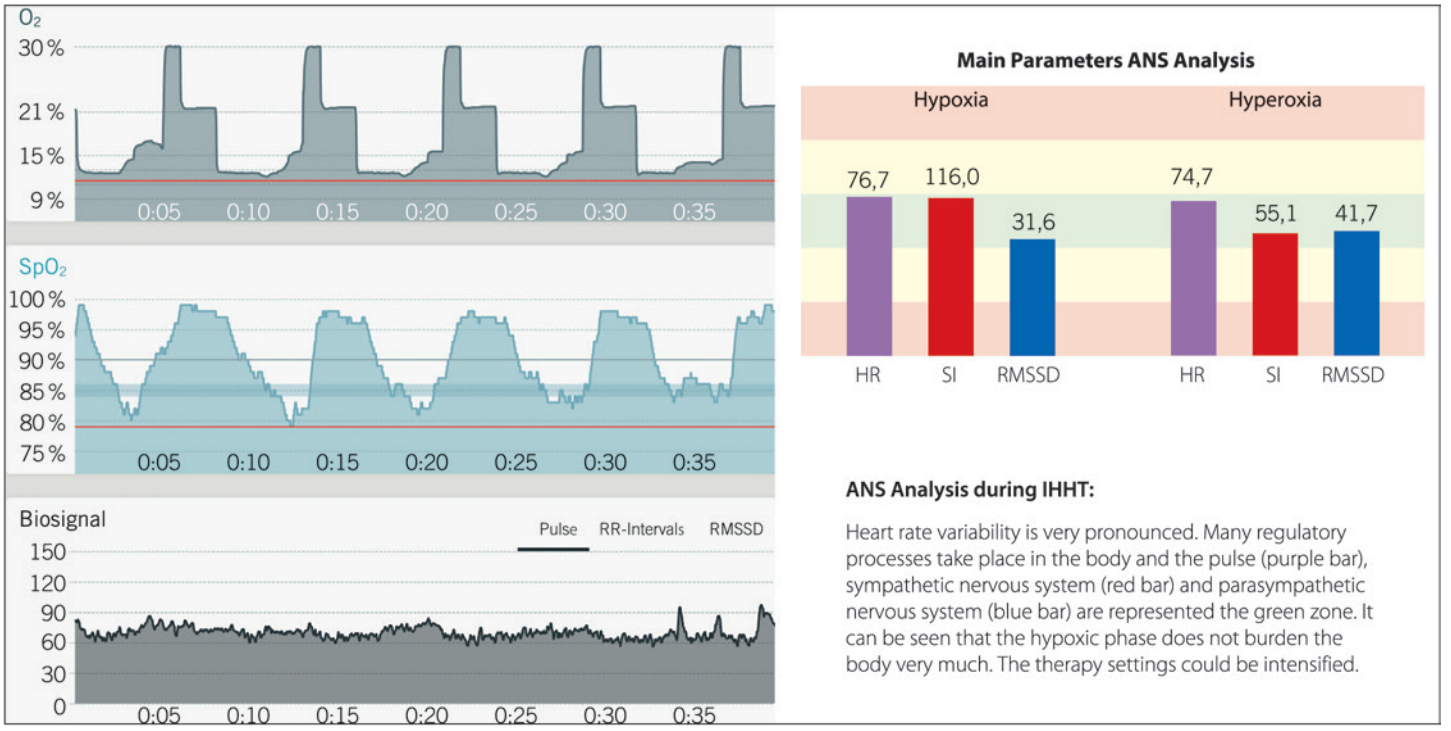
Selected indications in orthopaedics

Following a decline in the traumatic causes of orthopaedic illnesses as a result of traffic accidents, work-related accidents and warlike influences, the focus is now on the causes of illnesses resulting from modern lifestyles.
High stress, lack of exercise, hyperglycaemic diet, water contaminated with heavy metals, calcium channel-opening directed mobile phone radiation and environmental toxins are stressors for human cellular systems. The latest findings on the microbiome as a result of molecular-genetic examination possibilities, the close interactions with the human immune system, the findings on gut–brain axis as well as the new functional-medical examination possibilities on mitochondrial functional ion suggest that, in addition to tried and tested orthopaedicconservative therapies, treatment results should be improved by optimising mitochondrial processes.

Three common reasons for treatment are outlined below:

a. Chronified pain syndrome as a result of herniated disc for example

Chronic pain, e.g. as a result of a herniated disc with initially inconsistent therapy, is characterised by diagnostic and therapeutic resistance with changes in the psychomental programming of the patient, which make conventional treatment more difficult (Paulus, 2017, p. 25 and subsequent). The evaluation should take into account the duration, the spread of pain, the severity of pain-related limitations and the use of previous therapy and treatment options (Kröner-Herwig, 2018, p. 163). In addition to alleviating pain, improving movement and stress tolerance, therapeutic goals should include a reduction in vegetative derailment and an increase in mitochondrial performance. A combination of orthopaedic, movement therapy, psychological and nutrition therapy measures is often necessary (Kröner-Herwig, 2018, p.261 and subsequent).



Graphical evaluation of IHHT with MITOVIT®. Setting of biofeedback with adaptive hyperoxia: automatic adjustment of the O2 keeping the SpO2 between 90–79 %. The adaptive hyperoxia leads to a fast saturation of the blood oxygen by the hyperoxia and to a faster reaching of the training range through the normoxie phase since a supersaturation of oxygen is avoided. This further increases the success of the therapy.

Once the diagnosis has been completed, an effective therapy program could consist of the following therapy components:

1. patient eduction to change behaviour and to inform about the basically positive prognosis.

2. pain therapy by means of anti-inflammatory non-steroidal anti-inflammatory drugs (NSAIDs), preferably with retarded stomach-sparing preparations (e.g. "Arcoxia") and, if necessary, opiod analgesics to prevent further sensitisation to pain. Strict discipline must be observed when taking these drugs at fixed times.

3. computer-controlled traction therapy in the affected spinal segment (e.g. using a SpineMED traction couch)

4. If necessary, periradicular infiltration (e.g. as LSPA in Prof. Krämer's technique) of local anaesthetics for segmental densitisation of the nerve root, possibly once with cortisone to reduce the swelling of the nerve root.

5. carrying out the IHHT treatment.

Further meaningful therapy approaches can be acupuncture/laser acupuncture for detonation of permanently misdirected musculature due to nerve root affection. In addition, physiotherapy to learn a self-therapy program, relaxation methods such as progressive muscle relaxation, a diet rich in vitamins and minerals and depending on the mental/psychological status of the patients psychological care are possible therapy options. Among other things, IHHT contributes to creating an energy-rich basis for the patient to positively influence how pain is dealt with and to be able to cope better with everyday life. Patients, some of whom suffer significantly, quickly report a reduction in pain if the treatment is carried out consistently and often say in agreement with the IHHT treatment: "I simply have more strength". With IHHT it is possible to bring even chronic pain syndromes to healing relatively quickly or at least to a significant improvement.

b. Stress and muscle tension

In fact, many stress patients tend to go to an orthopaedist rather than a family doctor, neurologist, psychiatrist or internist because they primarily suffer from muscular tension. For this reason, the authors believe that it is imperative that conservative orthopaedists should also preferably deal with this topic.

In acute stress, the body focuses on being extremely efficient. By activating the sympathetic nervous system (stress nerve), an increase in blood pressure, an increased mobilisation of energy reserves and an expansion of the bronchi occurs. Furthermore, there is also a pre-tensioning of the musculature, which can lead to chronic tension and pain during prolonged stress due to the high consumption of energy (ATP) in addition to a reduction in performance (Litzcke et al., 2013, p. 22 and subsequent).

Muscular tension and back pain as a result of prolonged stress can be perceived as particularly strong due to reduced pain tolerance. The impairment of sleep further complicates the activation of the parasympathetic nervous system and the associated improvement of symptoms and stress (Kaluza, 2015, p. 210). Since stress leads to muscular tensions, but muscular tensions also lead to stress and further negative aspects such as lack of energy, high blood pressure and burnout can result, hence the treatment of muscular tensions and reduction of stress should be started early.

In addition to classical detonating measures such as manual therapy, massage therapy, osteopathy, wheals, neural therapy and infiltrations of the muscle trigger points as well as acupuncture or laser acupuncture, a holistic approach to therapy should be started as soon as the patient has been immediately removed from his stressful environment (e.g. issue of an incapacity for work certificate). IHHT plays an important role in this, as it generally starts at the cellular level. Mitochondrial therapy increasingly converts cellular energy production from sugar burning to fat burning. This enables the body to generate significantly higher energy to cope with its stress-adaptation reaction by optimizing oxidative phosphorylation.

Excessive oxygen radicals are reduced, the mitochondrial respiratory chain is optimized and, last but not least, the system of basic regulation according to Pischinger is shifted from the more gel-like to the liquid mode (Pischinger & Heine, 2014), so that all nutrients required by the cell can be better supplied and metabolic products better removed. The mental relaxation and quiet breathing (e.g. with the help of the app "Vagusvit") during the therapy contribute to the activation of the parasympathetic nervous system as a "relaxation nerve" and thus to an improvement of the medical conditions. The additional performance of a relaxation training can have a positive effect on the intensity of pain and the level of stress felt. This can be achieved, for example, by learning autogenic training or, as a simpler variant, by performing muscular relaxation training according to Jacobson. In addition, laboratory diagnostics should be carried out with regard to minerals and vitamins (in whole blood!) to compensate for any deficits. In particular vitamin D, co-enzyme Q10, vitamin C, biotin and vitamin B12, magnesium, manganese and iron should be examined. It is also important to support the microbiome, e.g. by administering appropriate pro- and prebiotics as electron donors, dietary fibres and immunomodulators. If the symptoms do not improve, an extended functional laboratory diagnosis should be used to rule out leaky-good syndrome or even leaky-brain syndrome or, if the findings are positive, to treat them accordingly.

c. Rheumatic diseases

Rheumatoid arthritis (RA – synonym of chronic polyarthritis) as an exemplary disease for the whole symptom complex of rheumatic diseases is a systemic inflammatory autoimmune disease which, if left untreated, is characterised by a progressive destruction of joints, tendon sheaths, bones and internal organs (Bernhard & Villiger, 2001, p.179). The triggers of RA represent both genetic and non-genetic factors, not all of which are yet known. In the meantime, a disease-causing change in the microbiome has been confirmed (Bernhard & Villiger, 2001, p. 179 & Lorenz, 2016, p. 16). In the development, an initial immune reaction is followed by a cascade of inflammatory processes (Bernhard & Villiger, 2001, p. 179 and subsequent). Changes in the musculoskeletal system can cause chronic pain, movement restrictions and functional restrictions. (Fiehn, 2014). Typical symptoms of RA are morning stiffness, swelling of joints and rheumatic nodes. The therapy focuses on a reduction of pain, alleviation of inflammation and movement to maintain muscles and mobility (Hammer, 2017).

Of course, a patient with rheumatoid arthritis belongs first to an internal or orthopaedic rheumatologist in order to carry out a therapy trial with appropriate anti-inflammatory medicines and eventually the prescription of drugs. In addition, physical therapy measures must be carried out in accordance with the current guidelines (Schneider et al., 2011).

Even with these symptoms, the implementation of IHHT treatment is a sensible therapy option. The chronic inflammatory cascade leads to a reduction in cellular ATP production in the mitochondria, which can be treated causally with IHHT. In this case, an additional therapy attempt should be made with high-dose vitamin C infusions, which can also achieve a therapy breakthrough in acute relapses in cortisone-resistant cases (Krebs, 2017, p. 244). However, it is important for practical implementation that vitamin C infusions and IHHT should not be carried out at the same time, as the antioxidant potentials add up, which could be unpleasant for the patient. It is recommended that IHHT and vitamin C high-dose infusions be administered at a later date. From a vitamin C dose of 15 g and above, care should also be taken to inject Co. enzyme Q in addition (Krebs, 2017, p. 26).

From the point of view of functional medicine, existing deficits in the vitamin and mineral balance must also be compensated for after appropriate laboratory chemical diagnostics, pathological microbial changes are be treated by administering suitable pre- and probiotics, immunomodulating therapies initiated and, if necessary, causes for existing oxidative or nitrosative stress are diagnosed and treated in accordance with the guidelines of functional medicine.

In this setting, the therapeutic possibilities of guideline-controlled rheumatology can be excellently combined with the therapeutic options of IHHT. The patient does not have to decide for or against a therapy concept, the combination provides the improvement. Since rheumatoid arthritis is a chronic systemic disease, it makes sense in this case to regularly refresh the status achieved by repeated IHHT sessions at intervals of e.g. 3 months. The intervals must be individually adapted to the specific clinical picture and, of course, the patient's resources.

d. Further fields of application: "high-altitude training" in sports medicine

An altitude training, which was imitated and optimized by IHHT, is used by competitive athletes, especially endurance athletes, to increase their performance. The effect of hypoxia is targeted in order to improve the oxygen transport capacity as a result of the increase in the number of erythrocytes (Friedmann & Bärtsch, 1997, p. 987). An orthopaedic practice is frequently visited by patients who practice a very extensive and performance-oriented sport and are restricted or prevented from doing so due to a wide variety of injuries. The non-invasive effects of IHHT can also be used to improve performance.

For the patients, in addition to rapid recovery with a return to performance-oriented sports, the preservation of physical performance during the convalescence period is of primary importance. IHHT makes it possible for athletes to complete height training in a relaxed sitting position during injury phases and to counteract a reduction in performance. The IHHT can also be included as a support during normal preparation for an important event, such as a competition. In addition to the positive effects of altitude training, the vegetative nervous system is also trained, which can, for example, shorten the regeneration time (activation of the parasympathetic nervous system).

Economic considerations – holistic biological medicine in modern orthopaedics

The Intermittent Hypoxia Hyperoxia therapy (IHHT) is a sensible therapy option in the orthopaedic-conservatively oriented specialist practice. Once the therapy indication has been determined by a specialist, 100 % of the further therapy can be delegated to suitable specialist personnel. As a result of the built-in safety mechanisms, the physician does not need to worry that damage to the patient may result from incorrect operation. In addition to the purchase or leasing of the equipment, a suitable rest room must be available and the use of an appropriate specialist must be taken into account financially. However, this is only required for the initial treatment over a period of approx. 10 minutes. Thereafter, the further therapy can take place unattended.

The patient also needs less than 5 minutes for subsequent treatments, so that the appropriate specialist is available for other measures. In control examinations using ANS analysis, this can also independently record measurement data after the system has been installed on the patient. A specialist on site is not necessary.

IHHT is not a service provided by the statutory health insurance funds. At present, it is not listed in Annex I of the federal and state aid regulations, so that it is fully reimbursed both by private health insurance companies and by the aid. In practice, a number combination
of the Physicians' Fee Schedule digits 646 (hypoxia test), 602 (oxymetric examination), 638 (punctual arterial and/or vein pulse writing) and 505 (respiratory therapy) has proved to be effective, enabling a turnover of approximately EUR 100.00 per session with the normal factors. With reduced factors it is usual to offer the therapy meeting to self payers for approx. 50,00 to 60,00 euro. It is also important that the corresponding four Physicians' Fee Schedule digits are not billed as analogue digits but as original Physicians' Fee Schedule digits with full service content, so that there are no formal reasons for individual payers to refuse cost reimbursment.

In the correlation between therapy costs and therapy fee, IHHT thus represents a form of therapy that is attractive not only from a professional but also from an economic point of view, and which to a large extent also includes a therapeutic unique selling point. It should not be underestimated that with this form of therapy not only orthopaedic clinical pictures but also other indications (e.g. sleep disorders, rehabilitation after heart attacks, COPD, CFS, etc.) can be treated, which can generate additional fees with an existing medical network.

Outlook

Chronic diseases resulting from secondary mitochondriopathies, i.e. diseases resulting from reactive mitochondrial dysfunction resulting from physiological and biochemical disturbances of the body, can become noticeable in the entire organism and are increasingly common in patients (Arnemann, 2018).

Among other things, they lead to an increasing incidence of diseases such as multiple sclerosis, rheumatic diseases, Parkinson's syndromes, dementia syndromes, depressive syndromes and metabolic diseases such as diabetes mellitus and hyperuricemia (Kuklinski, 2016). Mitochondrial dysfunction and disorders in the sensitive autonomic nervous system are increasingly influenced by stress, environmental and lifestyle factors.

Interval hypoxia-hyperoxia therapy as a non-invasive possibility to increase the efficiency of mitochondria and thus produce more energy in the form of adenosine triphosphate (ATP) is of interest to many medical specialties in the treatment of various diseases and as part of preventive measures. By training the vegetative nervous system and improving mitochondrial health , everyone can be supported in restful sleep, sufficient energy, pronounced stress resistance and normal functioning of the cardiovascular system. In medicine, IHHT could be an ideal supplement to conventional therapies and contribute to shortening the duration of treatment, improving the subjective state of health, slowing/stopping a negative course of the disease and preventing further diseases.

However, this requires new diagnostic thought patterns and effective and gentle therapy approaches without overemphasising surgical procedures and pharmacological strategies. IHHT in the context of functional medicine of the locomotor system meets these requirements and is also an economically attractive module in the portfolio of services offered by modern conservative orthopaedic practitioners.

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