HYPERBARIC OXYGENATION: RHEUMATOLOGY

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This review discusses different issues of hyperbaric oxygen therapy (HBOT) on rheumatology.

Basis. The clinical use of HBOT consists in breathing oxygen (O_2) at 100% in a pressurized chamber, of at least at 1.4 absolute atmospheres (ATA). Under these conditions, a large amount of O_2 is dissolved in the plasma and promptly used by all cells, reaching poorly perfused tissues.

Biochemical events. HBOT acts producing both hyperoxia and reactive oxygen species (ROS) and stimulating the activity of antioxidant systems. Hyperoxia triggers biochemical mechanisms, some of them, vasoconstriction, angiogenesis, osteogenesis, anti-inflammation and oxidative state modulation, stand out as therapeutic benefits in trauma diseases. Such biochemical markers are used to track beneficial events from HBOT, as they can vary by its therapeutic action.

Applications. Several indications of this therapy in various diseases are widespread and in continuous research and development. Literature is plenty of available scientific papers and protocols reporting HBOT uses in different specialties, including the clinical area, sport medicine, orthopedics, neurology and wounds recovery. In rheumatic diseases therapy, HBOT is used as adjuvant treatment, performing its therapeutical effect through alleviating pain, reducing inflammation, accelerating recovery, reducing the risk of infections and improving life quality.

Keywords: Hyperbaric Oxygenation, Chamber, Biomarkers, Rheumatology

Acronysms:

ATA: absolute atmospheres

CNS: central nervous system

EPO: erythropoietin

FR: free radicals

Hb: hemoglobin

HBO: hyperbaric oxygen

HBOT: hyperbaric oxygen therapy

HIF: hypoxia inducible factor

NO: nitric oxide

NOS: nitric oxide synthase

O_2: oxygen

Pp: partial pressure

PpO_2: oxygen partial pressure

$PtcO_2$: transcutaneous oxygen tension

ROS: oxygen reactive species

VEGF: vascular endotelial growth factor

1. Hyperbaric oxygen therapy: basis and oxygen physiology

HBOT consists in breathing O_2 near to 100% within a pressurized chamber above the normal atmospheric pressure (at sea level, or 1.0ATA). For clinical use, the pressure should be at least 1.4ATA [1]. Hyperbaric oxygenation (HBO) is used as a primary therapy [2], in certain diseases and intoxications, or as an adjunctive therapy in pathologies with inadequate oxygen supply to the tissues.

Physiology of oxygen

Hyperbaric chambers are medical devices where HBOT is performed in a non-invasive and safe fashion: high O_2 concentration is administered to the patient by means of a mask, within a pressurized environment. In order to understand how this therapy works, it is important to keep in mind the main function of the breathing process: oxygen enters the body, to be distributed throughout the circulatory system to all organs and tissues.

Physical basis

The physical-chemical basis of the therapy is essentially based on two physical laws that describe gas behavior. On one hand, Dalton's Law states that, at constant temperature, the total pressure of a gas mixture is equal to the addition of partial pressures (Pp) of each individual gas. In other words, each gas exerts a pressure proportional to its fraction in the total volume of the mixture [3]. Therefore, when using roughly 100%O_2 at 1.4ATA pressure, high PpO_2 is obtained, several times greater than in normal conditions (breathing normal air: 21%O_2, 1.0ATA). On the other hand, Henry's Law states that gases are dissolved in liquids when they are subjected to pressure: meaning that administered O_2 in a pressurized environment, is dissolved and distributed in the plasma and other fluids in contact with gas [3]. This effect takes place once the amount of inspired O_2 increases, generating a local pressure gradient in the alveoli, favoring the diffusion of oxygen into the plasma. Moreover, this mechanism is

independent from the transport of O_2 bound to hemoglobin (Hb), which is almost completely saturated (~97%) under physiological conditions [3].

The purpose of HBOT is to assure that O_2 enters the tissues, without the contribution of O_2 from Hb, in cases of obstruction of red blood cells flow (edema, inflammation) and in anemic patients [3]. Thus, most O_2 is dissolved in the plasma and a high concentration of circulating O_2 turns available to diffuse, reach and penetrate into tissues and cells.

Physiological basis

Once understood the diffusive behavior of O_2 in plasma, it is important to understand, through a model, how tissues and their cells receive O_2 during HBOT. The answer follows the Krogh model [4], which considers capillary density in tissues, capillary radius and the distance between cells and capillaries to calculate the O_2 diffusion distance and penetration. For example, depending on their function and metabolic rate, different organs and tissues of the organism have different density of blood vessels (capillaries and arterioles) per volume (100 to 3000 vessels/mm3) [4]. In addition, Krogh's model explains the existence of radial and longitudinal pressure gradients (PpO_2), depending on the radius of the capillary and the arterial and venous ends of the microvasculature, respectively (see figure 1). From the combination of these variables, the model allows prediction of PpO_2 in tissues: when O_2 is administered at a concentration near to 100% in a 1.4ATA environment, the O_2 penetration radius from capillaries to tissues is ~75μm.

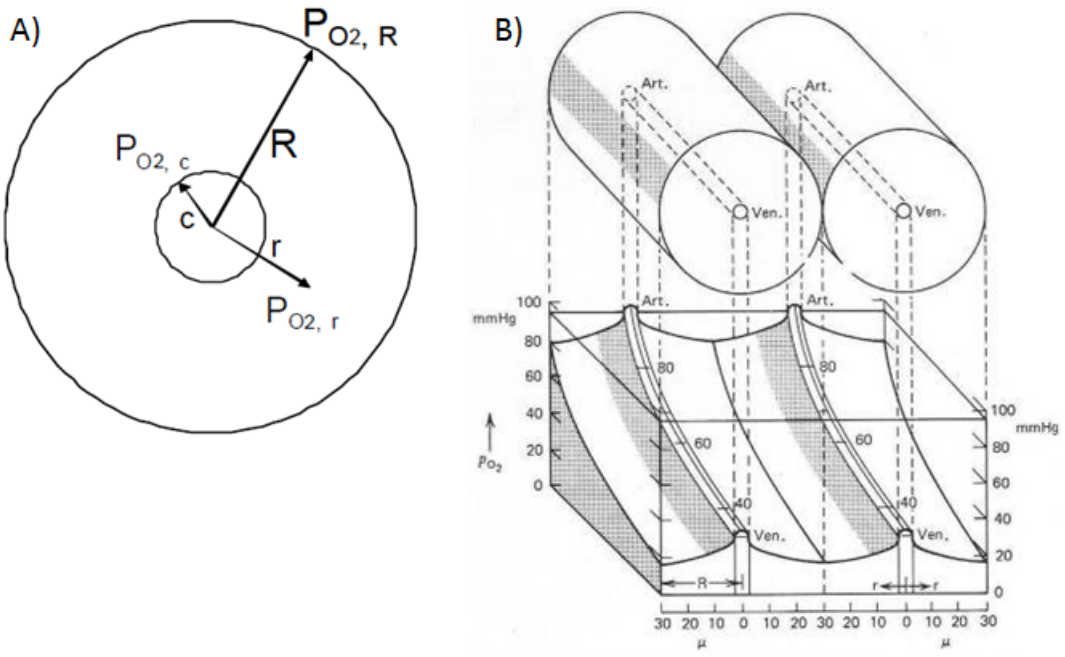

Figure 1. The Krogh model. A) Radius of capillary (c) and of a cylinder of tissue (R). PO_2 can be calculated at different points (c, r and R) and varies due to the existence of gradients. B) Scheme of PO_2 radial and longitudinal gradients, considering distance between adjacent capillaries [4].

Effective hyperbaria

It is important to remind the concept of effective hyperbaric and the clinical use definition for HBOT [1]. By administering O_2 at a concentration near to 100% at a pressure of 1.4ATA, arteriolar PpO_2 is approximately 918mmHg: a state of hyperoxia is achieved. This pressure is more than enough to ensure accurate O_2 supply to all tissues, through the diffusion and penetration of O_2 from the plasma to all cells, as indicated by the Krogh model (see Figure 2). In summary, under hyperbaric conditions (at least 1.4ATA), the O_2 penetration (~40μm) required to reach the minimum effective PpO_2 (20mmHg), needed to satisfy cellular functions, is achieved and exceeded considerably. Therefore, the clinical and physiological benefits of HBOT are manifested to 1.4ATA.

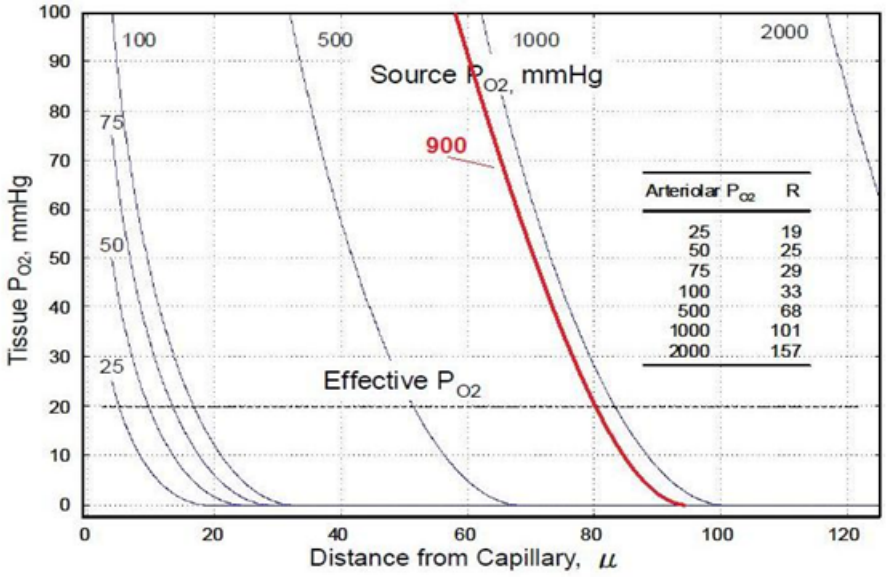

Figure 2. Effect of pressure treatment on diffusion profile and the maximum diffusion distance in a homogeneous medium. The PO_2 and O_2 penetration are estimated according to the distance R.

By analogy with drug therapy, HBOT should ensure that O_2 concentration is being maintained within the therapeutic window: overpass the minimum O_2 threshold needed to fulfill vital functions of aerobic cells, without exceeding high limits of O_2 concentrations, avoiding toxic effects due to the excessive production of reactive oxygen species (ROS).

2. Biochemical events

At the cellular level and under physiological conditions, O_2 is involved in multiple biochemical processes and reactions. The most important of these reactions is the production of energy through oxidative processes that converge in the synthesis of high energy bonds, as adenosine tri-phosphate (ATP). All life processes require energy to be executed.

The main beneficial effects of HBOT are related to O_2 transport, hemodynamics and immunological processes [3]. The action mechanism of HBOT is to produce hyperoxia and temporary increase the production of ROS [5]. Thus, it solves adverse conditions

such as hypoxia and edema, and promotes normal physiological responses or responses against infectious and ischemic processes [3]. Additionally to generate ROS and free radicals, HBOT stimulates the expression and activity of antioxidant enzymes, to maintain homeostasis and the redox cellular state (reductive/oxidative) and ensure treatment safety [3, 6].

Among the mechanisms promoted by HBOT in rheumatology, we can include:

Vasoconstriction. This effect is favored by increasing available O_2 in small arteries and capillaries. Vasoconstriction occurs in healthy tissue without deterioration in oxygenation, promoting flow redistribution to hypoperfused areas [3]. Therefore, the vasoconstriction produced is called "non hipoxemic", since it does not counteract the effect of hyperoxia. This vasoconstriction may also help to overcome mechanisms of vascular resistance present in different injuries [7], and is involved in the reduction and relief of pain, mediated by reduced levels of the vasodilator agent nitric oxide (ON) under hyperoxia [8].

Angiogenesis. Hyperoxia stimulates neovascularization, or the formation of new vessels, by two different processes: vasculogenesis and angiogenesis [6, 9, 10]. Angiogenesis is a regional process, driven by endothelial cells of blood vessels in regions affected by adverse events, injury or local hypoxia. Vasculogenesis is the *de novo* formation of blood vessels, favored by the stimulus of endothelial cells and new blood vessels cells on the formation, migration, recruitment and differentiation of stem or progenitor cells to the site of injury or hypoxia [6].

At a biochemical level, this mechanisms involves several growth factors, transcription factors, hormones and chemical mediators (HIF-1, EPO, VEGF, EGF, PDGF, IL) [5]. For example, sites of neovascularization generate ROS, stimulating the production of transcription factors (HIF-1: hypoxia inducible factor) [6], through HIF-1α and HIF-1β

subunits stabilization and dimerization [11]. HIF-1 stimulates the production of growth factors involved in neovascularization, such as VEGF (vascular endothelial growth factor) [6], for migration and differentiation of stem cells to endothelial cells [5, 9], and erythropoietin (EPO). While hypoxia is the major trigger mechanism of angiogenesis , if this condition is prolonged over time, the angiogenesis processes do not persist [9, 12, 13]. In particular, the pro-angiogenic effect triggered by HBOT is mediated by an increase of VEGF production [9], favoring the formation of new vessels after several sessions.

On the other hand, HBOT has effects on bone marrow, modulating the activity of nitric oxide synthase (NOS), which synthesizes nitric oxide (free radical, FR) and is involved in stem cell moving, favoring the healing process [6]. The angiogenesis process is known as a fundamental trophic mechanism, favored under hyperoxia, and potentially responsible for increased blood vessel density in hypoxic tissues [14].

Osteogenesis. The hyperoxia stimulates cell differentiation, formation of mineral reservoirs and phospho-calcium metabolism. The cell functions and bone remodeling carried out by osteogenic cells are O_2 dependent and are stimulated by the production of growth factors at hyperoxic conditions. The angiogenic effect and NO production also collaborate with bone formation and cell differentiation [15], through the mobilization of stem/progenitor cells. Through the combination of these mechanisms, HBOT favors the bone formation and repair, promotes necrotic bone resorption mediated by osteoclasts [3] and prevents progression to injuries and infections in trauma involving bone tissue.

Cellular immune response. In adverse conditions such as hypoxia, it can increase the predisposition to infections. Under hyperoxia conditions, some immune cells, such as neutrophils or polymorpho nuclear (PMN), respond to the presence of pathogens by

exerting their bactericidal action through the production of ROS, FR and peroxidase action [3]. These chemical mediators damage DNA and oxidize proteins and lipids (lipo-peroxidation), inhibiting bacterial metabolism. In this context, the attack against anaerobic micro-organisms, unable to produce their toxins under conditions of hyperoxia (α-toxins produced by spores of *clostridium perfringens*, causal agent of gas gangrene) takes place. In addition, HBOT with some antibiotics, exerts synergistic action facilitating O_2-dependent transport across the bacterial cell wall [3].

The HBOT effects on cellular immunity is manifested through the infection prevention and the reduction of cell mediated injury in ischemic tissues, without affecting the immune functions of white blood cells (WBC) (degranulation, phagocytosis), therefore it does not generate immune compromise to the patient [6, 16]. In this context, the exposure to HBO protects from injury by post-ischemic reperfusion (inhibiting β2-integrins synthesis, responsible for circulating neutrophils adhesion to vessels) [3] and thrombogenic effects (mediated by leukocytes) [5, 17]. In addition, the modulation of cellular immune response helps to alleviate the symptoms of infectious and autoimmune processes [16, 18, 19].

Anti-inflammation and edema reduction. Vasoconstriction helps to reduce the inflammation response and therefore to reduce edema [3], phenomena that are present in hypoxic and ischemic conditions [17]. In addition to the already mentioned processes (vasoconstriction and immunity), HBOT diminishes the production and release of pro-inflammatory cytokynes by neutrophils and monocytes [5, 17, 20]. Besides, HBO exposure contributes to edema and articular inflammation, favoring pain alleviation [21].

Markers

The HBOT follow-up includes clinical, biochemical and image studies for each specific pathology, together with general parameters that are affected by HBOT *per se*. These markers are sensitive to different pressures and for different pathologies [22-27].

These biochemical parameters can be classified according to the different hyperoxia mechanisms of action:

- Coagulation and hemostasis: KPTT, protrombin time, RIN, fibrinogen dosage, platelets, hepatic profile [28, 29]
- Acute phase reactant and inflammation markers: PCR, ceruloplasmin, integrin, cytokines, hematological profile [17, 23, 25, 30]
- Immunity: antibodies, cytokines, leukocytes, neutrophiles and limphocytes [16, 18, 19]
- Oxidative status: reactive O_2 metabolites, MDA, antioxidants (enzymatic: glutation peroxidase, superoxide dismutase, NOS, catalase, mieloperoxidase; non enzymatic: glutation, vitamins (C, A, E)) [17, 22-26, 30, 31]
- Bone formation/resorption: FAL, Osteocalcin, vitamin D, calcium, phosphorous, PTH, cross-laps [15, 32]
- Healing and angiogenesis: VEGF, collagen peptides, EPO [9, 23]

3. Trials

Several articles and reviews are available in the literature, including clinical trials, case reports, expert opinions and original research articles describing the effects and benefits of HBOT in patients, laboratory animals and model systems. Among works with patients, most of HBOT results derive from systematic reviews and randomized clinical trials (RCT) for several pathologies and at different pressures.

In addition to the applications of this therapy as a first-choice option (acute processes) or as an adjuvant therapy, complementary to other indications, HBOT shows great effectiveness when indicated at early stages and even in a preventive fashion [6, 11].

HBOT is usually indicated by specifying different variables that, together, determine the O_2 dose:

- Treatment pressure
- $\%O_2$ administered (continuous or at intervals)
- Session length: 60-90'
- Total number of sessions
- Daily/weekly frequency of sessions
- Total duration of sessions

In recent years, the treatment at pressures close to the minimum pressure requirement established by the Society of Hyperbaric Medicine (UHMS) [1] has been applied in various pathologies, around 1.4ATA, since it is safer, easier to apply and shows excellent therapeutic efficacy [22]. Next, we show the applications of HBOT on rheumatic diseases.

Table 1. Indications and statistics of cases treated with HBOT Revitalair chambers in rheumatology.

Disease	Number of cases	Therapeutic effctiveness	Indicated sessions (average)	Indicated frequency (average)	Sessiones compliance	Patient satisfaction	Sessions length (average)	Patient evolution
Rheumatoid arthritis	59	88%	28	3	90%	93%	70 min.	86%
Arthrosis	26	89%	28	4	85%	85%	67 min.	93%
Bone edema	6	92%	35	5	83%	83%	64 min.	100%
Fibromyalgia	69	86%	31	4	90%	71%	64 min.	86%
Disc protrusion	23	93%	30	3	91%	83%	67 min.	96%
Osteomyelitis	4	100%	30	3	100%	100%	68 min.	100%
Bone necrosis	9	99%	26	5	100%	89%	65 min.	100%

HBOT in rheumatic diseases

In particular, HBOT is widely used for the treatment of inflammatory conditions, such as those affecting bone tissues, motor system, connective tissue and joints. These rheumatic diseases are usually treated in a multidisciplinary way, in which therapeutic strategies focus on reducing inflammation, pain and improving the quality of life.

In hypoxic situations, the low pO_2 hypoxia state is responsible for cellular damage and perfusion alterations [33]. Under hypoxic conditions, angiogenesis becomes slower and even null, it diminishes the function of fibroblasts and the formation of collagen is compromised [34]. At the cellular level, hyperoxia solves all these functions, since they are O_2-dependent. TOHB plays an important protective role during situations of ischemia and hypoxia, through the action of hyperoxia reducing lipid peroxidation during ischemia-reperfusion processes [20, 33].

In disabling pathologies such as rheumatoid arthritis (RA), characterized by the presence of pain and deterioration of life quality, the use of HBOT could favor pain relief and decrease inflammation in joints [21]. The disease relief by the action of HBOT can be produced by an increase in the enzymatic antioxidant capacity, which favors a decrease in lipid peroxides [31]. For example, the treatment for patients with RA with HBOT, gives good clinical results, both immediately and at long-term [19], due to the relief of systemic symptoms and the modulation of the immune response.

In other rheumatic diseases, with inflammatory and autoimmune components, such as systemic lupus erythematosus (SLE), it was observed that HBOT is able to inhibit the action of some pro-inflammatory cytokines, acting as immune-modulator [18]. In patients with SLE and/or scleroderma, HBOT improves cognitive dysfunction. In patients with SLE, fibromyalgia syndrome (FMS) and chronic fatigue, alterations in

cerebral perfusion were detected, which could be treated and improved through the use of HBOT [18].

Particularly, in patients with FM, HBOT can improve symptoms and life quality, due to perfusion improvement and normalization of activity in brain areas related to pain [35]. The pain relief favored by HBOT in FM, is related to its ability to stimulate angiogenesis, mediated by VEGF [36].

HBOT is also effective for the treatment of aggressive, bone-affecting infections, difficult and ineffectively treated by the hard access of antibiotics to bone tissue. In the course of pathologies such as osteomyelitis (OM), tissular pO_2 is very low, due to trauma, vascular compromise and fibrosis. The use of HBOT increases pO_2, necessary for neo-vascularization, reversal of ischemia, acceleration of healing, growth inhibition of anaerobic microorganisms by stimulation of the phagocytic action of leukocytes in hypoxic tissues, promotion of osteogenesis and activation of osteoclasts in the removal of bone debris [15, 37-39]. A complete eradication of the infection was observed thanks to the adjuvant use of HBOT, showing its efficacy in the management of refractory chronic OM, by favoring the success of conventional surgical and clinical treatments [37]. HBOT displays direct and indirect antimicrobial effects and attenuates the systemic inflammatory response, helping to delimit viable tissue of the non-viable ones, reducing the extent of debridement, amputations and morbi-mortality [40]. In situations of bone necrosis, early damage to the microcirculation may occur, requiring restoration of bone oxygenation. The use of TOHB in these conditions promotes collagen synthesis, proliferation of fibroblasts, neo-vascularization and reduction of edema, thanks to vasoconstriction and increased tissue oxygenation [39].

HBOT is indicated in patients with inflammatory, hypoxic and/or autoimmune pathologies to maintain tissue viability and aerobic metabolism, reduce edema and

improve perfusion, avoid ischemia-reperfusion injury, favor host response against infections, improve healing, reduce amputations and complications [40].

In summary, HBOT is used as an adjuvant treatment in rheumatology to relieve pain, modulate the immune response, reduce the inflammation, the risk of infections and amputations, accelerate recovery, reconstitute perfusion and improve life quality [8, 21, 31, 35, 37, 39].

CONCLUSIONS

HBO is successful and widely used as primary or adjuvant therapy in different pathologies. Its effectiveness is based on the generation of hyperoxia, from which multiple physiological benefits are triggered for the patient. Many of the biochemical effects and mechanisms favored by hyperoxia can be evidenced through the monitoring of biochemical markers. These markers are sensitive to the therapeutic action of HBO at different pressures and in different pathologies, showing changes mainly in antioxidant system and anti-inflammatory response.

Given the mechanism of action of HBOT, its application is approved for pathologies of varied origin, framed in different medical specialties. Its use is in constant research and growth phase. There is a great amount and variety of trials describing the effects of HBOT in different specialties and pathologies. Both in daily practice and in the development of clinical trial, it is important to consider, in particular, the duration of each session and the number and frequency of weekly sessions for each specific disease.

In rheumatology, HBOT proved to be useful in solving ischemia and hypoxia, reducing edema and improving perfusion, decreasing the occurrence of complications and infections, accelerating recovery, relieving pain and improving life quality. Particularly,

it is used as an adjuvant treatment of autoimmune pathologies, connective tissue, chronic pain and bone infections.

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