HYPERBARIC OXYGENATION: SPORT MEDICINE

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

**Basis.** The clinical use of HBOT consists in breathing oxygen (O₂) at 100% in a pressurized chamber, of at least at 1.4 absolute atmospheres (ATA). Under these conditions, a large amount of O₂ 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, anti-inflammation, oxidative state modulation, fibroblast stimulation and cell mediated immune response, stand out as benefits in sport medicine. 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 sport medicine, HBOT is used as adjuvant treatment, performing its therapeutical effect through hypoxia reversion, improvement in vascularization, sportive performance and healing acceleration.

**Keywords:** Hyperbaric Oxygenation, Chamber, Biomarkers, Sport Medicine
Acronyms:
ATA: absolute atmospheres
EPO: erythropoietin
FR: free radicals
Hb: hemoglobin
HBO: hyperbaric oxygen
HBOT: hyperbaric oxygen therapy
HIF: hypoxia inducible factor
NOS: nitric oxide synthase
O₂: oxygen
Pp: partial pressure
PpO₂: oxygen partial pressure
PtcO₂: transcutaneous oxygen tension
ROS: oxygen reactive species
VEGF: vascular endotelial growth factor
1. Hyperbaric oxygen therapy: basis and oxygen physiology

HBOT consists in breathing O₂ 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 O₂ 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%O₂ at 1.4ATA pressure, high PpO₂ is obtained, several times greater than in normal conditions (breathing normal air: 21%O₂, 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 O₂ 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 O₂ 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\textsubscript{2} bound to hemoglobin (Hb), which is almost completely saturated (~97%) under physiological conditions [3]. The purpose of HBOT is to assure that O\textsubscript{2} enters the tissues, without the contribution of O\textsubscript{2} from Hb, in cases of obstruction of red blood cells flow (edema, inflammation) and in anemic patients [3]. Thus, most O\textsubscript{2} is dissolved in the plasma and a high concentration of circulating O\textsubscript{2} turns available to diffuse, reach and penetrate into tissues and cells.

**Physiological basis**

Once understood the diffusive behavior of O\textsubscript{2} in plasma, it is important to understand, through a model, how tissues and their cells receive O\textsubscript{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\textsubscript{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/mm\textsuperscript{3}) [4]. In addition, Krogh’s model explains the existence of radial and longitudinal pressure gradients (PpO\textsubscript{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\textsubscript{2} in tissues: when O\textsubscript{2} is administered at a concentration near to 100% in a 1.4ATA environment, the O\textsubscript{2} penetration radius from capillaries to tissues is ~75\textmu m.
Effective hyperbaria

It is important to remind the concept of effective hyperbaric and the clinical use definition for HBOT [1]. By administering O\textsubscript{2} at a concentration near to 100% at a pressure of 1.4ATA, arteriolar PpO\textsubscript{2} is approximately 918mmHg; a state of hyperoxia is achieved. This pressure is more than enough to ensure accurate O\textsubscript{2} supply to all tissues, through the diffusion and penetration of O\textsubscript{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\textsubscript{2} penetration (~40µm) required to reach the minimum effective PpO\textsubscript{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.
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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].

During sportive exercise, an accurate O₂ supply is not only necessary, but also indispensable to ensure physical performance under intense activities. The hyperoxia favors the performance and energy reserves, through increased muscle fibers oxygenation [7]. The increase O₂ availability in tissues saturates myoglobin and allows to maintain O₂ intracellular reservoirs, improving muscular performance and power during contraction [8]. The hyperoxic state also promotes better energy performance and prevents muscle mass working under anaerobic conditions, preventing or decreasing lactic acid formation. In addition, by reducing the cellular need for O₂ supply, hyperoxia helps to decrease heart rate (HR) and to increase ventilatory capacity [9, 10].

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

**Vasoconstriction.** This effect is favored by increasing available O₂ 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.

**Angiogenesis.** Hyperoxia stimulates neovascularization, or the formation of new vessels, by two different processes: vasculogenesis and angiogenesis [6, 11, 12]. 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
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*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 [13]. 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], and erythropoietin (EPO). While hypoxia is the major trigger mechanism of angiogenesis [11], if this condition is prolonged over time, the angiogenesis processes do not persist [11, 14, 15]. In particular, the pro-angiogenic effect triggered by HBOT is mediated by an increase of VEGF production [11], 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].

**Cellular immune response.** In adverse conditions such as hipoxia, susceptibility to infections increases. In hyperoxia, some immune cells such as neutrophils or polymorphonuclear cells (PMN) respond to pathogenic noxa exerting its bactericidal action, through ROS and FR production and peroxidase enzymes activity [3]. These chemical mediators damage DNA and oxidize proteins and lipids (lipid peroxidation), inhibiting bacterial metabolism. In this context, the attack against anaerobes is reinforced, because they are unable to produce their toxins in hyperoxic conditions (α-
toxins produced during *clostridium perfringens* sporulation in gas gangrene). Furthermore, HBOT exerts synergistic action with some antibiotics facilitating O₂-dependent transport through 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]. 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].

**Collagen synthesis.** Collagen is a structural protein synthesized by fibroblasts by complex chemical reactions, including hydroxylation of proline and lysine amino acids. The hydroxylation reaction and cross-linking of the collagen fibers, are favored in the presence of high O₂ concentrations (peptides and propeptides collagen) [5].

**Anti-inflammation and edema reduction.** Vasoconstriction helps to reduce the inflammatory response and therefore to reduce edema [3]. HBOT diminishes production and release of pro-inflammatory cytokynes by neutrophils and monocytes [5].

**Cell proliferation and differentiation.** Collagen synthesis and extracellular matrix formation is produced by fibroblast proliferation, favoring the formation of scar tissue and new vessels, looking to resolve hypoxic conditions and tissue hypoperfusion injury. This effect is also mediated by the increased synthesis of growth factors favored by HBOT through FR and ROS. In addition to stem/progenitor cells and new vessels, components such as collagen are essential in the mainly proliferative and remodeling phases, during the healing process [12].
Wound healing. Along with stimuli which promote collagen synthesis and neovascularization, hyperoxia also stimulates the formation of granulation tissue in regions affected by adverse conditions. Through the synergy between these mechanisms, the process of wound healing is accelerated.

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 [16-21]. 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 [22, 23]
- Acute phase reactant and inflammation markers: PCR, ceruloplasmin, integrin, cytokines, hematological profile [17, 19]
- Metabolism: lactic acid, blood glucose, pH [9, 10, 20]
- Oxidative status: reactive O$_2$ metabolites, MDA, antioxidants (enzymatic: glutation peroxidase, superoxide dismutase, NOS, catalase, mieloperoxidase; non enzymatic: glutation, vitamins (C, A, E)) [10, 16-20, 22]
- Healing and angiogenesis: VEGF, collagen peptides, EPO [11, 17]

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, 13].

HBOT is usually indicated by specifying different variables that, together, determine the O₂ dose:

- Treatment pressure
- %O₂ administered (continuous or at intervals)
- Session length: 60-90'
- Total number of sessions
- Daily/weekly frequency of sessions
- Total duration of sessions

When HBOT is indicated for sport medicine conditions, it is necessary to consider factors as how much time after training, recovery or injury has elapsed, because the earlier beginning the better the results. The treatment schedule will depend on the phase in which it is required to apply HBOT: training, recovery, competition and/or injury. This type of patients requires constant medical control, so the duration, amount and frequency of sessions can vary from one athlete to another, or from one phase to another. In particular, the total duration of HBOT in sports medicine is variable, depending on the severity of the injury and the usual recovery time of different events and/or injuries. Whenever possible, it is advisable to use 90' sessions in these patients, aiming to maximize tolerance to physical activity and shortening recovery times.

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 [16].

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of cases</th>
<th>Therapeutic effectiveness</th>
<th>Indicated sessions (average)</th>
<th>Indicated frequency (average)</th>
<th>Session compliance</th>
<th>Patient satisfaction</th>
<th>Sessions length (average)</th>
<th>Patient evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle contracture</td>
<td>7</td>
<td>82%</td>
<td>14</td>
<td>4</td>
<td>71%</td>
<td>71%</td>
<td>63 min.</td>
<td>93%</td>
</tr>
<tr>
<td>Muscle tear</td>
<td>56</td>
<td>94%</td>
<td>29</td>
<td>4</td>
<td>98%</td>
<td>96%</td>
<td>58 min.</td>
<td>92%</td>
</tr>
<tr>
<td>Sprain</td>
<td>5</td>
<td>100%</td>
<td>14</td>
<td>4</td>
<td>100%</td>
<td>100%</td>
<td>65 min.</td>
<td>100%</td>
</tr>
<tr>
<td>Sport recovery</td>
<td>79</td>
<td>93%</td>
<td>19</td>
<td>3</td>
<td>92%</td>
<td>87%</td>
<td>57 min.</td>
<td>96%</td>
</tr>
<tr>
<td>Tendon injury</td>
<td>5</td>
<td>100%</td>
<td>25</td>
<td>3</td>
<td>100%</td>
<td>100%</td>
<td>68 min.</td>
<td>100%</td>
</tr>
</tbody>
</table>

**HBOT in sport medicine**

Next, we discuss the uses and benefits of hyperbaric therapy on this specialty. The HBO treatment in sport medicine has different objective. The HBOT is widely used for the prevention, treatment and recovery of training or injuries produced during physical exercise.

In particular, it is used for a) the physical preparation of athletes for high performance; B) the recovery of physical exercise and the prevention of fatigue, in periods of intense activity (before, during or after participating in competitions) [7-9, 24]; C) treatment and recovery of traumatic injuries related to sports practice [24-27].

In figure 3 we summarize the main effects and benefits of HBOT for athletes, both for training and recovery phases. Through all these mechanisms, triggered by hyperoxia, the athlete achieves greater tolerance to exercise and less physical and muscular fatigue [8, 28], maximizing its performance and shortening the recovery time [9]. In addition, HBOT allows to better and faster healing of injured tissues, shortening sport inactivity time [26].
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Figure 3. Main effects and benefits of HBOT in sports medicine.

The HBOT favors performance improvement during physical exercise because, by increasing pO$_2$, it increases maximal ventilatory capacity and O$_2$ uptake, promotes and improves O$_2$ diffusion in skeletal muscle and minimizes the production of lactic acid [9, 10, 20]. Through these mechanism, HBO increases the anaerobic threshold, decreases heart rate and, by favoring energy production and reservoirs in muscles, prevents muscle fatigue, cramps and tears in athletes [9, 10]. By increasing the supply of O$_2$ to muscles under contraction, HBO favors exercise tolerance and reduces the cellular alteration produced by exercise at maximum intensity [10, 28]. The exposure to HBO can improve muscle strength in short-term and intense exercise [9].

The application of HBOT seeks to maximize physical and muscular performance, minimize edema, prevent fatigue, shorten recovery period and, in case of injury, preserve tissue viability, protect microvasculature, improve immune response and promote wound closure.
Used as adjuvant therapy, HBOT can benefit each of these issues directly: performance, recovery and healing. The HBOT is promising to treat sports injuries [27], accelerate recovery time, reduce inactivity time [26, 29], improve ventilatory capacity and tolerance to intense exercise (see Figure 3) [28]. In addition, the benefits of early use of HBOT considerably reduce complications on ligament and tendon injuries [24], through different mechanisms triggered by hyperoxia, related to the resolution of injuries and wounds and to healing acceleration.

**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 sports medicine, TOHB has been shown to be useful favoring energy performance and rehabilitation and, in sports injuries, resolving ischemia and hypoxia, to allow
reincorporation of the athlete to physical exercises. The HBOT is used to prepare the athlete during training, shorten recovery, prevent fatigue and heal trauma and injuries.

REFERENCES


