HYPERBARIC OXYGENATION: TRAUMATOLOGY

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

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, osteogenesis, anti-inflammation, oxidative state modulation and neuroprotection, 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 trauma treatment, HBOT is used as adjuvant treatment, performing its therapeutical effect through recovery acceleration, alleviating pain, reducing inflammation and the risk of infections and amputation, improving life quality.

Keywords: Hyperbaric Oxygenation, Chamber, Biomarkers, Traumatology
**Acronyms:**

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  
O₂: oxygen  
Pp: partial pressure  
PpO₂: oxygen partial pressure  
PtcO₂: transcutaneous oxygen tension  
ROS: oxygen reactive species  
VEGF: vascular endothelial 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 ($P_p$) 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 $P_pO_2$ 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 O₂ bound to hemoglobin (Hb), which is almost completely saturated (~97%) under physiological conditions [3].

The purpose of HBOT is to assure that O₂ enters the tissues, without the contribution of O₂ from Hb, in cases of obstruction of red blood cells flow (edema, inflammation) and in anemic patients [3]. Thus, most O₂ is dissolved in the plasma and a high concentration of circulating O₂ turns available to diffuse, reach and penetrate into tissues and cells.

**Physiological basis**

Once understood the diffusive behavior of O₂ in plasma, it is important to understand, through a model, how tissues and their cells receive O₂ 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 O₂ 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 (PpO₂), 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 PpO₂ in tissues: when O₂ is administered at a concentration near to 100% in a 1.4ATA environment, the O₂ 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 traumatology, 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 neurological 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-1\(\alpha\) and HIF-1\(\beta\)
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 O₂ 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.** 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 \(\beta_2\)-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].

**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 at central nervous system (CNS) [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, 18]. Besides, HBO exposure contributes to edema reduction and intracranial pressure alleviation [17, 18].

**Neuroprotection.** Among the mechanisms involved in neuroprotection displayed by HBOT, it is important to highlight the preservation of cellular energy production and reservoirs, regulation of oxidative stress and decreasing of neutrophil accumulation and adhesion [17-19]. At the mitochondrial level, HBOT is able to restore the polarization and permeability of the mitochondrial membrane, improving efficiency in energy production and modulation of ROS levels [17, 20, 21]. In addition, by favoring vasoconstriction and anti-inflammation, hyperoxia helps to decrease intracranial pressure and cerebro-spinal fluid volume [17, 22]. These effects, together with improved tissue oxidation and normalization of the oxidative state at the mitochondrial level, help to preserve neuronal function and activity and to protect against apoptosis [17, 20, 22]. TOHB is also able to stimulate and favor neuroplasticity, through restoring oxygenation, from chronically inactive areas affected by neuronal injuries [23]. The
Hyperbaric oxygenation favors the release of stem/progenitor cells from the bone marrow to the peripheral circulation and to the CNS, favoring neurogenesis [14].

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 [24-29]. 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 [30, 31]
- Acute phase reactant and inflammation markers: PCR, ceruloplasmin, integrin, cytokines, hematological profile [17, 21, 25, 27]
- Oxidative status: reactive O\(_2\) metabolites, MDA, antioxidants (enzymatic: glutation peroxidase, superoxide dismutase, NOS, catalase, mieloperoxidase; non enzymatic: glutation, vitamins (C, A, E)) [17, 21, 24-28]
- Bone formation/resorption: FAL, Osteocalcin, vitamin D, calcium, phosphorous, PTH, cross-laps [15, 32]
- Healing and angiogenesis: VEGF, collagen peptides, EPO [9, 25]

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 \([24]\).

Next, we show the applications of HBOT on trauma.

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

<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>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>Non-union</td>
<td>12</td>
<td>89%</td>
<td>31</td>
<td>3</td>
<td>75%</td>
<td>100%</td>
<td>64 min.</td>
<td>98%</td>
</tr>
<tr>
<td>Disc protrusion</td>
<td>23</td>
<td>93%</td>
<td>30</td>
<td>3</td>
<td>91%</td>
<td>83%</td>
<td>67 min.</td>
<td>96%</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>1</td>
<td>100%</td>
<td>20</td>
<td>3</td>
<td>100%</td>
<td>100%</td>
<td>65 min.</td>
<td>100%</td>
</tr>
<tr>
<td>Post-surgical</td>
<td>40</td>
<td>96%</td>
<td>11</td>
<td>4</td>
<td>92%</td>
<td>95%</td>
<td>67 min.</td>
<td>99%</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 traumatology

In particular, TOHB is widely used for the treatment of trauma from different origins, affecting different organs and tissues. Some injuries require surgery and can be treated with HBOT, including acute traumatic ischemia, compartment syndrome, compromised grafts and flaps, infectious processes and traumatic burns [33].

The traumas compromise health of the traumatized patient, since the triggering of a state of regional or systemic hypoxia, affecting the perfusion of some tissues and, therefore, their viability [33, 34]. Under hypoxic conditions, angiogenesis becomes slower and even null, aggravates fibroblast function and collagen formation is compromised [35]. At the cellular level, hyperoxia solves all these functions, since they are O2-dependent.

In situations of injury and cerebral ischemia, the state of hypoxia is responsible for neuronal damage, inefficient synapses and alterations in perfusion [35]. These phenomena are due to altered metabolism and neuronal activity during hypoxia [20].

The aim of therapies for cerebral ischemia is to rescue normal tissue, which is under risk of irreversible damage due to O2 deprivation of and the consequent energetic and metabolic alteration. Therefore, therapeutic measures focus on improving blood flow and preserving cellular function [36]. In this context, HBOT plays an important role in neuronal protection during ischemia, through the action of hyperoxia reducing lipid peroxidation in ischemia and ischemia-reperfusion processes [18, 37]. The HBOT can reduce the inflammatory state and cerebral edema, favoring the repair of axons, stimulating their growth and maintaining the blood-brain barrier integrity [17, 18, 20, 38].

The exposure to HBO also favors the redistribution of cerebral blood flow, relieving intracranial pressure and its symptoms [8, 39]. It attenuates motor deficits, reduces the
Hyperbaric oxygenation: traumatology

Hyperbaric oxygenation: traumatology

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reduce amputations, complications and peripheral nerve injuries, accompanying these trauma [33].

In summary, TOHB is used as adjuvant treatment in traumatology to accelerate recovery, relieve pain, reduce inflammation, risk of infections and amputations, reconstitute perfusion, improve neuronal recovery and quality of life [14, 18, 21, 29, 33-35, 40, 43]. The results of HBO therapy in patients with peripheral trauma, brain and spinal cord injury are promising and deserve further research.

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 trauma, have proved that HBOT is useful resolving ischemia and hypoxia, reducing edema and improving perfusion, decreasing the occurrence of complications and neuronal sequelae, accelerating recovery and improving quality of life. In particular, it
is used as an adjuvant treatment of ischemic and infectious injuries, affecting bones, muscles, brain and spinal cord.

REFERENCES


