HYPERBARIC OXYGEN THERAPY IN MUSCLE INJURIES

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ABSTRACT
Oxygen is a drug with several therapeutic applications. Hyperbaric Oxygen Therapy (HBO) consists in the administration of oxygen, at pressures superior than 1 atmosphere inside a sealed chamber. The growing interest on HBO generated many studies that demonstrated its clinical interest in several pathologies and its safety. In the field of muscle injuries treatment, HBO is promising but more studies are necessary.

KEYWORDS
Hyperbaric oxygen therapy, muscle injuries.

RESUMO
O oxigénio é um fármaco com inúmeras aplicações terapêuticas. A Oxigenoterapia Hiperbárica consiste na administração de oxigénio, a pressões superiores a 1 atmosfera dentro de uma câmara hermética. O crescente interesse pela Oxigenoterapia Hiperbárica tem levado a diversos estudos que demonstram o seu interesse terapêutico em diversas patologias e a sua segurança. No campo do tratamento de lesões musculares a OTH parece ser promissora mas são necessários mais estudos nesta área.

PALAVRAS-CHAVE
Oxigenoterapia hiperbárica, lesões musculares

1. **INTRODUCTION**

Hyperbaric oxygen therapy (HBO) is a treatment, in which patients breathe pure oxygen (or sometimes other gas mixtures) intermittently while inside a treatment chamber at a pressure higher than sea level pressure.

HBO has a number of physiological and pharmacological modes of action. These therapeutics mechanisms of action are based on elevation of both the partial pressure of oxygen and hydrostatic pressure (Thom, "Oxidative"). These properties constitute the rationale for treatment of a number of different conditions.

HBO originated from the treatment of decompression illness over a hundred years ago. During the last fifty years, several other indications for hyperbaric therapy have been proposed (De Laet et al.).

The administration of pure oxygen under atmospheric pressures higher than sea level has been proposed to address a wide variety of medical and surgical problems for many decades (Grim et al.; Tibbles and Edelsberg). However, a sense of controversy continues to pervade the field of hyperbaric medicine. Only a restricted number of indications have been accepted by the two main scientific hyperbaric societies, because there is a lack of evidence in many subjects. However, there are ongoing international studies, aiming to clarify the efficacy of HBO for other specific indications.

Hyperbaric therapy units are managed by different medical specialities, depending on its indication. Many of the units are primarily military, mostly in the navy, for historical reasons, due to the need for a treatment facility of diving incidents. Apart from this, most units are linked to departments of anaesthesiology. There is a high interest in physics, gas laws, and pharmacology and physiology, and many units treat patients requiring intensive care therapy (Mortensen). This review aims to present Hyperbaric Medicine and its fundaments and also its application in the field of muscle injuries treatment.

2. **DEFINITION**

Hyperbaric therapies are methods used to treat diseases or injuries using pressure higher than local atmospheric pressure inside a hyperbaric chamber. Within hyperbaric therapies, Hyperbaric Oxygen Therapy (HBOT) is the administration of pure oxygen (100%) at pressures greater than atmospheric pressure for therapeutic reasons (De Laet et al.). It is defined by the Undersea and Hyperbaric Medical Society (UHMS) as "a treatment in which a patient breathes 100% oxygen while inside a treatment chamber at a pressure higher than sea level pressure, i.e. more than 1 atmosphere absolute (ATA)" (Undersea & Hyperbaric Medical Society).

3. **CONDITIONS FOR HYPERBARIC OXYGEN ADMINISTRATION**

To be able to perform HBO, installations are required, with the capacity of withstanding pressures higher than the atmospheric - hyperbaric chambers – where patients breathe 100% oxygen (Fernandes).

At case of single seat chambers (capacity for only one person - monoplace) the oxygen is inhaled directly from the environment chamber (Fernandes). Although much less expensive to install and support, they have the major disadvantage of impossible access to the patient during treatment. It is possible to monitor a cuff blood pressure, arterial waveform, electrocardiogram, and to provide intravenous medications and fluids. Mechanical ventilation is possible if chambers are appropriately equipped, although it is not possible to suction patients during treatment. Mechanical ventilation in the monoplace chamber is provided by a modified pressure-cycled ventilator outside of the chamber (Sheridan and Shank).

In multiplace chambers, the internal atmosphere is room air compressed up to 6 atmospheres. Attendants in this environment breathe compressed air, accruing a nitrogen load in their soft tissues, just as a scuba diver breathing compressed air. These attendants need to decompress to avoid the decompression illness by using more complex decompressure procedures when the treatment tables are more extend (e.g. Navy Tables). The patients, on the other hand, are breathing oxygen while at pressure. This oxygen can be administered via face mask, a hood or endotracheal tube. The advantage of such a chamber is that the patient can be attended during treatment, but the installation and support costs are very high. These high costs preclude the widespread use of multiplace chambers (Sheridan and Shank).

4. **BIOCHEMICAL, CELLULAR AND PHYSIOLOGICAL EFFECTS**

The level of consumption of O_2 by a given tissue, on the local blood stream, and the relative distance of the zone considered from the nearest arteriole and capillary determines the O_2 tension in this tissue. Indeed, O_2 consumption causes oxygen partial pressure (pO_2) to fall rapidly between arterioles and veinules. This emphasizes the fact that in tissues there is a distribution of oxygen tensions according to a gradient. That also exists at the level of the cell such as in the mitochondrion, the terminal place of oxygen consumption, where O_2 concentrations range from 1.5 to 3 μM (Mathieu).

Before reaching the sites of utilization within the cell like perioxome, mitochondria, endoplasmic reticulum, the oxygen moves down a pressure gradient from inspired to alveolar gas, arterial blood, the capillary bed, across the interstitial and intercellular fluid. Under normobaric conditions, the gradient of pO_2 known as the "oxygen cascade" starts at 21.2kPa (159mm Hg) and ends up at 0.5-3kPa (3.8-22.5mm Hg) depending on the target tissue (Mathieu). The arterial oxygen tension (PaO_2) is approximately 90 mm Hg and the tissue oxygen tension (PtO_2) is approximately 55 mm Hg (Sheridan and Shank). These values are markedly increased by breathing pure oxygen at greater than atmospheric pressure.

Hyperbaric oxygen therapy is limited by toxic oxygen effects to a maximum pressure of 300kPa (3 bar). Partial pressure of carbon dioxide in the arterial blood ($PaCO_2$), water vapor pressure and respiratory quotient (RQ) do not vary significantly between 100kPa and 300kPa (1 - 3bar). Thus, for example, the inhalation of 100% oxygen at 202.6kPa (2ATA) provides an alveolar PO_2 of 1423mm Hg and, consequently, the alveolar oxygen passes the alveolar--capillary space and diffuses into the venous pulmonary capillary bed according to Fick's Laws of Diffusion (Mathieu).

4.1. **HYPEROXIGENATION**

Oxygen is transported by blood in two ways: chemically, bound to the hemoglobin and physically dissolved in plasma. During normal breathing, or the environment we live in, hemoglobin has an oxygen saturation of 97%, representing a total oxygen content of about 19.5 O_2/100ml of blood (or 19.5vol%), because 1g of 100% saturated hemoglobin carries 1.34ml oxygen. In these conditions the amount of oxygen dissolved in plasma is 0.32vol%, giving a total of 19.82vol% oxygen. When we offer 100% oxygen through a Hudson mask, or endotracheal intubation for a patient breathing, the oxygen content can reach values up to 22 to 22.2vol% (Jain).

The principle effect of HBO is hyperoxia. During this therapy, oxygen is dissolved physically in the blood plasma. At an ambient pressure of 2.8 ATA and breathing 100% oxygen, the alveolar oxygen tension (PAO_2) is approximately 2,180 mm Hg, the PaO_2 is at least 1,800 mm Hg, and the tissue concentration (PtO_2) is at least 500 mm Hg. The oxygen content of blood is approximately ([1.34 x Hbg x SaO_2] + [0.0031 x PaO_2]), where Hbg is serum hemoglobin concentration and SaO_2 is arterial oxygen saturation (Sheridan and Shank). At a PaO_2 of 1,800 mm Hg, the dissolved fraction of oxygen in plasma (0.0031 x PaO_2) is approximately 6vol%, which means that 6ml of oxygen will be physically solved in 100ml of plasma, reaching a total volume of oxygen in the circulating blood volume equal to 26.9vol%, equivalent to basic oxygen metabolic needs, and the PaO_2 in the arteries can reach 2,000 mmHg. With a normal lung function and tissue perfusion, a pO_2 > 1,000 mmHg could be reached (Mayer et al.). Breathe pure oxygen environment at 2 ATA, the oxygen content in plasma is 10 times higher that breathing air at sea level. Under normal conditions the partial pressure of oxygen in the blood (pO_2) is 95mmHg, under conditions of a hyperbaric chamber, the pO_2 can reach values greater than 2000mmHg (Jain). Consequently, during HBO, Hbg is also fully saturated on the venous side, and the result is an increased oxygen tension throughout the vascular bed. Since diffusion is driven by a difference in tension, oxygen will be forced further out into tissues from the vascular bed (Mortensen) and diffuses to areas inaccessible to molecules of this gas when transported by hemoglobin erythrocyte (Albuquerque e Sousa).

After removal from the hyperbaric oxygen environment, the PaO_2 normalizes in minutes, but the PtO_2 may remain elevated for a variable period. The rate of normalization of PtO_2 has not been clearly described, but is likely measured in minutes to a few hours, depending on tissue perfusion (Sheridan and Shank).

The physiological effects of HBO include short-term effects like vasoconstriction and enhanced oxygen delivery, reduction of edema, and phagocytosis activation, and it has an anti-inflammatory effect (enhanced leukocyte function). Neovascularization (angiogenesis in hypoxic soft tissues), osteoneogenesis as well as stimulation of collagen production by fibroblasts are the known long-term effects. This is beneficial for wound healing and recovery of radiation-injured tissue (Mayer et al.; Sheridan and Shank).

4.2. **VASOCONSTRICTION**

In normal tissues, the primary action of oxygen is to cause general vasoconstriction (especially in the kidneys, skeletal muscle, brain and skin), which elicits a "Robin Hood effect" through a reduction of blood flow to well oxygenated tissue (Mortensen). The HBO not only provides a significant increase availability of molecular oxygen at the tissue, as hyperoxic

not hypoxic vasoconstrict, selective, occurring predominantly at the level of healthy tissues, with reduced blood volume and redistribution edema for peripheral tissue hypoxia, which raises the anti-ischemic and anti-hypoxic effects to extremities as physiological mechanism (Albuquerque e Sousa). HBO reduces oedema, partly because of vasoconstriction, partly due to improved mechanisms of homeostasis. A high gradient of oxygen is a potent stimulator of angioneogenesis, which has an important contribution in the stimulation of reparative and regenerative processes in some conditions (Mortensen).

4.3. **LEUKOCYTE OXIDATIVE KILLING**

Many cell and tissue functions are depending on oxygen. Of special interest are leukocyte ability to kill bacteria, cell replication, collagen formation, and mechanisms of homeostasis, such as active membrane transport, e.g. the sodium–potassium pump. HBO has the effect of inhibiting leukocyte adhesion to endothelium, diminishing tissue damage, which enhances leukocyte motility and improve microcirculation (Mortensen). This occurs when the presence of gaseous bubbles in the venous vessels blocks the flow and induces hypoxia which causes endothelial stress followed by the release of nitric oxide (NO) that reacts with superoxide anion to form peroxynitrine. This, in turn, provokes oxidative perivascular stress and leads to the activation of leukocytes and their adhesion to the endothelium (Antonelli et al.).

4.4. **NEOVASCULARIZATION/ANGIOGENESIS**

Hypoxia is the major factor stimulating angiogenesis. However, deposition of collagen is increased by hyperoxygenation, and is the collagen matrix that provides the support base for the growth of new capillary bed. Two hours daily treatments with HBO are apparently responsible for stimulating the oxygen in the synthesis of collagen, the remaining 22h of hypoxia real or relative, in which the patient is not subjected to HBO, provide the stimulation of angiogenesis. Thus, the alternation of states of hypoxia and hyperoxia, observed in patients during treatment with intermittent HBO is responsible for maximum stimulation of fibroblast activity in ischemic tissues, producing the development of the matrix of collagen, essential for neovascularization (Jain).

The presence of oxygen, not only has the advantage of promoting an environment less hospitable to anaerobes, but also is known to speed the process of wound healing, whether from being required for the production of collagen matrix and subsequent angiogenesis, from the presence and beneficial effects of reactive oxygen species (ROS), or from yet undetermined means (Kunnavatana et al.).

Dimitrijevich et al. studied the effect of HBO on human skin cells in culture and in human dermal and skin equivalents. In that study, normal human dermal fibroblasts, keratinocytes, melanocytes, dermal equivalents, and skin equivalents were exposed to HBO at pressures up to 3 ATA for up to 10 consecutive daily treatments lasting 90 minutes each. An increase in fibroblast proliferation, collagen production, and keratinocyte differentiation was observed at 1 and 2.5 ATA of HBO, but no benefit at 3 ATA. Kang et al. reported that HBO treatment up to 2.0 ATA enhances proliferation and autocrine growth factor production of normal human fibroblasts grown in a serum-free culture environment, but showed no benefit beyond or below 2 ATA of HBO. Therefore a delicate balance between having enough and too much oxygen and/or atmospheric pressure is needed for fibroblast growth (Kunnavatana et al.).

4.5. **ANTIMICROBIAL EFFECT**

HBO, by reversing tissue hypoxia and cellular dysfunction, restores this defense and also increases the phagocytic capacity of some bacteria by working synergistically with antibiotics, and inhibiting growth of a number of anaerobic and aerobic organisms at wound site (Mader et al.). There is evidence that hyperbaric oxygen is bactericidal for *Clostridium perfringens*, besides promoting a definitive inhibitory effect on the growth of toxins in most aerobic and microaerophilic microorganisms. The action of HBO on the anaerobes is based in the formation of free radicals like superoxide, dismutase, catalase and peroxidase. There have been identified over 20 different clostridial exotoxins, and the most prevalent is the alfatoxine (fosfolipase C), which is hemolytic, tissue necrotizing, and lethal. Other toxins, acting in synergy, promote anemia, jaundice, renal failure, cardiotoxicity and brain dysfunction. The thetatoxine is responsible for vascular injury and consequent acceleration of tissue necrosis. HBO blocks the production of alfa and thetatoxine and inhibits bacterial growth (Jain).

5. **HBO IN TREATMENT OF MUSCLE INJURIES**

There are many accepted indications with different levels of evidence for treatment using HBO. Accepted indications can be found at the European Committee for Hyperbaric Medicine and at Undersea & Hyperbaric Medical Society.

Hyperbaric Oxygen has often also been suggested as an effective treatment for sports injuries in general and muscle injuries in particular, as first suggested by Oriani et al.

Human and animal models have demonstrated promising results, namely in what concerns healing acceleration. Temple University (Potera) conducted a study in ankle sprains in which athletes treated with HBO recovered 30% faster than the control group, even if the sample size was small and big variability was found.

In animals forced to eccentric work, namely the downhill running model, it was found that HBO was able to play an inhibitory effect on the inflammatory process and hence to modulate the injury to the tissue (Staples et al., "The effects of intermittent hyperbaric oxygen on biochemical").

Similarly, in a study performed in humans, HBO demonstrated to be able to enhance the recovery of eccentric strength from a delayed onset muscle soreness injury but had no effect on pain (Staples, "The effects of intermittent hyperbaric oxygen on pain").

Also studies, both performed in animals (Horn et al.) and humans (Staples, "The effects of intermittent hyperbaric oxygen on pain") demonstrated that HBO seems to able to enhance recovery of ligament strength after serious injuries, with both positive effects in pain decrease and functional outcomes. Mashitori et al. reported that type I procollagen gene expression 7 days after injury was significantly higher in the HBO treated group, suggesting that HBO is useful for medical treatment of injuries of this type.

On the other hand, a different animal study, conducted by Harrison et al., examined the effects of treating exercise induced muscle injury using HBO and did not found significant benefits from using HBO. This study is also supported by another one, performed in humans

by Staples and Clement that treated patients with muscular pain in the quadriceps, reporting no large difference in the recovery in the group treated with HBO, especially in what concerned subjective sharp pain.

In one of the rare studies performed in high level athletes' ever published (Ishii et al.) HBO was used as a recovery method from muscular fatigue occurred during the Nagano Winter Olympics. In this experiment seven Olympic athletes received HBO treatment during 30-40 min at 1.3 ATA with a maximum of six times per athlete and an average of two. It was found that all players benefited from the conditioning effects of HBO treatment. Previously Fischer et al. reported that HBO treatment was able to remove ammonia from blood leading to a quicker recovery from fatigue. These data were confirmed by Haapaniemi et al. that added that also lactic acid was eliminated faster with HBO treatment, even if these results were not supported by those published by Rozenek et al.

A Meta-Analysis performed by Bennett et al. that was meant to examine the effect of HBO on Delayed Onset Muscle Soreness induced in subjects found no evidence of improved speed recovery and indication of increased interim pain during recovery. Even if in many studies it was found some evidence of the possible benefits of HBO, the meta-analysis pointed many flaws in the studies methodologies with a common problem being related to sample size.

Two major mechanisms seem to be involved in the treatment benefits due to HBO treatment: enhancement healing of the cellular damage initiated by the injury and/or an attenuation of the free radical damage. The first mechanism is based in the fact that inflammatory response following injury increases oxygen demand at the wound site and in traumatic injury oxygen delivery is decreased due to disruption of local microcirculation (Staples and Clement). HBO is known to decrease oedema by reducing capillary pressure, thus decreasing the distance for oxygen diffusion from the capillaries that had been increased by the generated oedema. HBO is also known to increase microvasculature thus decreasing inflammatory response. Additionally it seems that hyperoxigenation stimulates collagen synthesis and an augmentation of collagen deposition combined with vessel growth processes contributes to the enhanced healing from HBO (Abbot et al.).

Other authors (Boykin et al.) suggest that neutrophil production of free radicals may be important in leading to tissue destructive events occurring from ischemia and that injured tissues have an impaired metabolism that makes them hypoxic. This situation makes the cells unprotected from the highly reactive products created by neutrophil burst generated during the injury. This generates a vicious cycle of neutrophil adhesion and continued endothelial disruption (Bird and Telfer). HBO prevents excess neutrophils and other particles to clutter in the injured area, thus promoting a faster healing, the major benefit of HBO being the removing of free radicals that are very damaging to the tissue and that can be responsible for chronic inflammation (Thom, "Functional"). So far the best explanation for this phenomenon is a combination between the vasoconstrictive properties of HBO, free-radical removal, reduction of neutrophil adhesion and enhancement of leukocyte killing.

6. **CONCLUSION**

HBO is being increasingly used in the treatment of a number of areas of medical practice even without a comprehensive understanding of its healing mechanisms. Though some

critics have been raised on the safety of this treatment, evidence is demonstrating its safety. Some interesting results have been presented for the use of HBO for treating muscle injuries but those studies presented either study design flaws or small sample sizes, so more and more detailed studies are needed.

7. **REFERENCES**

Abbot, N. C., et al. "Effect of Hyperoxia at 1 and 2 ATA on Hypoxia and Hypercapnia in Human Skin during Experimental Inflammation." *Journal of Applied Physiology* 77.2 (1994): 767-73.

Albuquerque-e-Sousa, J. G. "Oxigenoterapia hiperbárica (OTHB). Perspectiva histórica, efeitos fisiológicos e aplicações clínicas." *Revista da Sociedade Portuguesa de Medicina Interna* 14.4 (2007): 219-27.

Antonelli, C., et al. "Guiding Principles in Choosing a Therapeutic Table for DCI Hyperbaric Therapy." *Minerva Anestesiologica* 75.3 (2009): 151-61.

Bennett, M., et al. "Hyperbaric Oxygen Therapy for Delayed Onset Muscle Soreness and Closed Soft Tissue Injury." *Cochrane Database Syst Rev* 19.4 (2005): s.p.

Bird, A. D., and A. B. Telfer. "Effect of Hyperbaric Oxygen on Limb Circulation." *Lancet* 1.7381 (1965): 355-56.

Boykin, J. V., E. Eriksson, and R. N. Pittman. "In Vivo Microcirculation of a Scald Burn and the Progression of Postburn Dermal Ischemia." *Plastic and Reconstructive Surgery* 66.2 (1980): 191-98.

De Laet, C., et al. "Hyperbaric Oxygen Therapy: a Rapid Assessment." *KCE Report 74C*. Brussels: Belgian Health Care Knowledge Centre (KCE) - Health Technology Assessment (HTA), 2008.

Dimitrijevich, S. D., et al. «Effect of Hyperbaric Oxygen on Human Skin Cells in Culture and in Human Dermal and Skin Equivalents." *Wound Repair and Regeneration* 7.1 (1999): 53-64.

European Committee for Hyperbaric Medicine, European Committee for Hyperbaric Medicine (ECHM). 11 Ago. 2010. 6 Maio 2010 <http://www. http://www.echm.org >.

Fernandes, T. D. "Medicina hiperbárica." *Acta Medica Portuguesa* 22 (2009): 323-34.

Fischer, B., et al. *Handbook of Hyperbaric Oxygen Therapy*. s.l.: Springer-Verlag, 1988.

Grim, P. S., et al. «Hyperbaric Oxygen Therapy." *Jama* 263.16 (1990): 2216-21.

Haapaniemi, T., et al. "Hyperbaric Oxygen Treatment Attenuates Glutathione Depletion and Improves Metabolic Restitution in Postischemic Skeletal Muscle." *Free Radical Research* 23.2 (1995): 91-101.

Harrison, B.C., et al. «Treatment of Exercise-Induced Muscle Injury Via Hyperbaric Oxygen Therapy." *Medicine & Science in Sports & Exercise* 33.1 (2001): 36-42.

Horn, P. C., et al. «The Effect of Hyperbaric Oxygen on Medial Collateral Ligament Healing in a Rat Model." *Clinical Orthopaedics and Related Research* 360. (1999): 238-42.

Ishii, Y., et al. "Hyperbaric Oxygen as an Adjuvant for Athletes." *Sports Medicine* 35.9 (2005): 739-46.

Jain, K. K. "Textbook of Hyperbaric Medicine." *Military Medicine* s.nº (2004): s.p.

Kang, T. S., et al. "Effect of Hyperbaric Oxygen on the Growth Factor Profile of Fibroblasts." *Archives of Facial Plastic Surgery* 6.1 (2004): 31-35.

Kunnavatana, S. S., et al. "Combined Effect of Hyberbaric Oxygen and N-Acetylcysteine on Fibroblast Proliferation." *Archives of Otolaryngology-Head & Neck Surgery* 131.9 (2005): 809-14.

Mader, J. T., et al. "A Mechanism for the Amelioration by Hyperbaric Oxygen of Experimental Staphylococcal Osteomyelitis in Rabbits." *The Journal of Infectious Diseases* 142.6 (1980): 915-22.

Mashitori, H., et al. "Effect of Hyperbaric Oxygen on the Ligament Healing Process in Rats." *Clinical Orthopaedics and Related Research* 423 (2004): 268-74.

Mathieu, D. *Handbook on Hyperbaric Medicine*. Dordrecht: Kluwer Academic Pub, 2006.

Mayer, R., et al. "Hyperbaric Oxygen and Radiotherapy." *Strahlentherapie und Onkologie* 181.2 (2005): 113-23.

Mortensen, C. "Hyperbaric Oxygen Therapy." *Current Anaesthesia & Critical Care* 19.5-6 (2008): 333-37.

Oriani, G., et al. "HBO Therapy in Treatment of Various Orthopaedic Disorders." *Minerva Med* 73 (1987): 2983-88.

Potera, C. "Healing Under Pressure." *Phys Sportsmed* 23.11 (1995): 46-47.

Rozenek, R., et al. "Does Hyperbaric Oxygen Exposure Affect High-Intensity, Short-Duration Exercise Performance?" *The Journal of Strength & Conditioning Research* 21.4 (2007): 1037-41.

Sheridan, R.L., and E. S. Shank. "Hyperbaric Oxygen Treatment: a Brief Overview of a Controversial Topic." *The Journal of Trauma* 47.2 (1999): 426-35.

Staples, J., and D. Clement. "Hyperbaric Oxygen Chambers and the Treatment of Sports Injuries." *Sports Medicine* 22.4 (1996): 219-27.

Staples, J. R. *The Effects of Intermittent Hyperbaric Oxygen on Pain Perception and Eccentric Strength in a Human Injury Model*. Diss. U British Columbia, Canada, 1996.

Staples, J. R., et al. «The Effects of Intermittent Hyperbaric Oxygen on Biochemical Muscle Metabolites of Eccentrically-Exercised Rats." *Can J Appl Physiol* 20 1995: 49P.

Thom, S. R. "Functional Inhibition of Leukocyte B2 Integrins by Hyperbaric Oxygen in Carbon Monoxide-Mediated Brain Injury in Rats." *Toxicology and Applied Pharmacology* 123.2 (1993): 248-56.

Thom, S. R. "Oxidative Stress is Fundamental to Hyperbaric Oxygen Therapy." *Journal of Applied Physiology (Bethesda, Md.: 1985)* 106.3 (2009): 988-995.

Tibbles, P. M., and J. S. Edelsberg. "Hyperbaric-Oxygen Therapy." *The New England Journal of Medicine* 334.25 (1996): 1642-48.

Undersea & Hyperbaric Medical Society, Undersea & Hyperbaric Medical Society. 2007. 6 May 2010 <http://www.uhms.org>.