Hyperbaric oxygen effects on sports injuries

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***Abstract*:** In the last decade, competitive sports have taken on a whole new meaning, where intensity has increased together with the incidence of injuries to the athletes. Therefore, there is a strong need to develop better and faster treatments that allow the injured athlete to return to competition faster than with the normal course of rehabilitation, with a low risk of re-injury. Hyperbaric therapies are methods used to treat diseases or injuries using pressures higher than local atmospheric pressure inside a hyperbaric chamber. Within hyperbaric therapies, hyperbaric oxygen therapy (HBO) is the administration of pure oxygen (100%) at pressures greater than atmospheric pressure, i.e. more than 1 atmosphere absolute (ATA), for therapeutic reasons. The application of HBO for the treatment of sports injuries has recently been suggested in the scientific literature as a modality of therapy either as a primary or an adjunct treatment. Although results have proven to be promising in terms of using HBO as a treatment modality in sports-related injuries, these studies have been limited due to the small sample size, lack of blinding and randomization problems. HBO seems to be promising in the recovery of injuries for high-performance athletes; however, there is a need for larger samples, randomized, controlled, double-blinded clinical trials combined with studies using animal models so that its effects and mechanisms can be identified to confirm that it is a safe and effective therapy for the treatment of sports injuries.

***Keywords*:** hyperbaric oxygen therapy, sports injuries

Introduction

In the last decade, competitive sports have taken on a whole new meaning, where intensity has increased together with the incidence of injuries to the athletes. These sport injuries, ranging from broken bones to disrupted muscles, tendons and ligaments, may be a result of acute impact forces in contact sports or the everyday rigors of training and conditioning [Babul *et al.* 2003].

Therefore, a need has emerged to discover the best and fastest treatments that will allow the injured athlete to return to competition faster than the normal course of rehabilitation, with a low risk of re-injury.

Hyperbaric oxygen therapy (HBO) is the therapeutic administration of 100% oxygen at pressures higher than 1 absolute atmosphere (ATA). It is administered by placing the patient in a multiplace or in a monoplace (one man) chamber and typically the vessels are pressurized to 1.5–3.0 ATA for periods between 60 and 120 minutes once or twice a day [Bennett *et al.* 2005a]. In the monoplace chamber the patient breathes the oxygen directly from the chamber but in the multiplace chamber this is done through a mask. At 2.0 ATA, the blood oxygen content is increased 2.5% and sufficient oxygen becomes dissolved in plasma to meet tissue needs in the absence of haemoglobin-bound oxygen, increasing tissue oxygen tensions 10-fold (1000%) [Staples and Clement, 1996]. HBO is remarkably free of untoward side effects. Complications such as oxygen toxicity, middle ear barotrauma and confinement anxiety are well controlled with appropriate pre-exposure orientations [Mekjavic *et al.* 2000].

HBO has been used empirically in the past, but today information exists for its rational application. This review aims to analyse the contribution of HBO in the rehabilitation of the different sports injuries.

Hyperbaric oxygen therapy

Hyperbaric therapies are methods used to treat diseases or injuries using pressures higher than local atmospheric pressure inside a hyperbaric chamber. Within hyperbaric therapies, HBO is

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the administration of pure oxygen (100%) at pressures greater than atmospheric pressure, i.e. more than 1 ATA, for therapeutic reasons [Albuquerque e Sousa, 2007].

In order to be able to perform HBO, special facilities are required, with the capacity for withstanding pressures higher than 1 ATA, known as hyperbaric chambers, where patients breathe 100% oxygen [Fernandes, 2009].

In the case of single monoplace chambers (with a capacity for only one person) the oxygen is inhaled directly from the chambers' environment [Fernandes, 2009]. Although much less expensive to install and support, they have the major disadvantage of not being possible to access the patient during treatment. It is possible to monitor blood pressure, arterial waveform and electrocardiogram noninvasively, and to provide intravenous medications and fluids. Mechanical ventilation is possible if chambers are equipped appropriately, 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, 1999].

In multiplace chambers, the internal atmosphere is room air compressed up to 6 ATA. Attendants in this environment breathe compressed air, accruing a nitrogen load in their soft tissues, in the same way as a scuba diver breathing compressed air. These attendants need to decompress to avoid the decompression illness by using more complex decompression procedures when the treatment tables are more extended (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 to during treatment, but the installation and support costs are very high. These high costs preclude the widespread use of multiplace chambers [Sheridan and Shank, 1999].

Biochemical, cellular and physiological effects of HBO

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 vennules. This emphasizes the fact that in tissues there is a distribution of oxygen tensions according to a gradient. This also occurs at the cell level such as in the mitochondrion, the terminal place of oxygen consumption, where O_2 concentrations range from 1.5 to 3 μM [Mathieu, 2006].

Before reaching the sites of utilization within the cell such as the perioxome, mitochondria and 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 21.2 kPa (159 mmHg) and ends up at 0.5–3 kPa (3.8–22.5 mmHg) depending on the target tissue [Mathieu, 2006]. The arterial oxygen tension (PaO_2) is approximately 90 mmHg and the tissue oxygen tension (PtO_2) is approximately 55 mmHg [Sheridan and Shank, 1999]. These values are markedly increased by breathing pure oxygen at greater than atmospheric pressure.

HBO is limited by toxic oxygen effects to a maximum pressure of 300 kPa (3 bar). Partial pressure of carbon dioxide in the arterial blood ($PaCO_2$), water vapour pressure and respiratory quotient (RQ) do not vary significantly between 100 and 300 kPa (1 and 3 bar). Thus, for example, the inhalation of 100% oxygen at 202.6 kPa (2 ATA) provides an alveolar PO_2 of 1423 mmHg 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, 2006].

Hyperoxya and hyperoxygenation

Oxygen is transported by blood in two ways: chemically, bound to haemoglobin, and physically, dissolved in plasma. During normal breathing in the environment we live in, haemoglobin has an oxygen saturation of 97%, representing a total oxygen content of about 19.5 ml O_2/100 ml of blood (or 19.5 vol%), because 1 g of 100% saturated haemoglobin carries 1.34 ml oxygen. In these conditions the amount of oxygen dissolved in plasma is 0.32 vol%, giving a total of 19.82 vol% oxygen. When we offer 85% oxygen through a Hudson mask or endotracheal intubation the oxygen content can reach values up to 22.2 vol% [Jain, 2004].

The main 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 2180 mmHg, the PaO_2 is at least 1800 mmHg and the tissue concentration (PtO_2) is at least 500 mmHg. The oxygen content of blood is approximately
$([1.34 \times Hbg \times SaO_2] + [0.0031 \times PaO_2])$,
where Hbg is serum haemoglobin concentration and SaO_2 is arterial oxygen saturation [Sheridan and Shank, 1999]. At a PaO_2 of 1800 mmHg, the dissolved fraction of oxygen in plasma ($0.0031 \times PaO_2$) is approximately 6 vol%, which means that 6 ml of oxygen will be physically dissolved in 100 ml of plasma, reaching a total volume of oxygen in the circulating blood volume equal to 26.9 vol%, equivalent to basic oxygen metabolic needs, and the paO_2 in the arteries can reach 2000 mmHg. With a normal lung function and tissue perfusion, a partial pressure of oxygen in the blood (pO_2) > 1000 mmHg could be reached [Mayer *et al.* 2004]. Breathing pure oxygen at 2 ATA, the oxygen content in plasma is 10 times higher than when breathing air at sea level. Under normal conditions the pO_2 is 95 mmHg; under conditions of a hyperbaric chamber, the pO_2 can reach values greater than 2000 mmHg [Jain, 2004]. 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, 2008] and diffuses to areas inaccessible to molecules of this gas when transported by haemoglobin [Albuquerque e Sousa, 2007].

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, 1999].

The physiological effects of HBO include short-term effects such as vasoconstriction and enhanced oxygen delivery, reduction of oedema, phagocytosis activation and also an anti-inflammatory effect (enhanced leukocyte function). Neovascularization (angiogenesis in hypoxic soft tissues), osteoneogenesis as well as stimulation of collagen production by fibroblasts are known long-term effects. This is beneficial for wound healing and recovery from radiation injury [Mayer *et al.* 2004; Sheridan and Shank, 1999].

Physiological and therapeutic effects of HBO

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, 2008]. HBO not only provides a significant increase in oxygen availability at the tissue level, as selective hyperoxic and not hypoxic vasoconstriction, occurring predominantly at the level of healthy tissues, with reduced blood volume and redistribution oedema for peripheral tissue hypoxia, which can raise the anti-ischemic and antihypoxic effects to extremities due to this physiological mechanism [Albuquerque e Sousa, 2007]. HBO reduces oedema, partly because of vasoconstriction, partly due to improved homeostasis mechanisms. A high gradient of oxygen is a potent stimuli for angioneogenesis, which has an important contribution in the stimulation of reparative and regenerative processes in some diseases [Mortensen, 2008].

Also many cell and tissue functions are dependent on oxygen. Of special interest are leukocytes 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 the endothelium, diminishing tissue damage, which enhances leukocyte motility and improves microcirculation [Mortensen, 2008]. 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) which reacts with superoxide anions 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.* 2009].

Another important factor is hypoxia. Hypoxia is the major factor stimulating angiogenesis. However, deposition of collagen is increased by hyperoxygenation, and it is the collagen matrix that provides support for the growth of new capillary bed. Two-hour daily treatments with HBO are apparently responsible for stimulating the

oxygen in the synthesis of collagen, the remaining 22 h of real or relative hypoxia, in which the patient is not subjected to HBO, provide the stimuli for 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, 2004].

The presence of oxygen has the advantage of not only promoting an environment less hospitable to anaerobes, but also speeds 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.* 2005].

Dimitrijevich and colleagues studied the effect of HBO on human skin cells in culture and in human dermal and skin equivalents [Dimitrijevich *et al.* 1999]. 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 and colleagues 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 [Kang *et al.* 2004]. Therefore, a delicate balance between having enough and too much oxygen and/or atmospheric pressure is needed for fibroblast growth [Kunnavatana *et al.* 2005].

Another important feature to take into account is the potential antimicrobial effect of HBO. HBO, by reversing tissue hypoxia and cellular dysfunction, restores this defence and also increases the phagocytosis of some bacteria by working synergistically with antibiotics, and inhibiting the growth of a number of anaerobic and aerobic organisms at wound sites [Mader *et al.* 1980]. There is evidence that hyperbaric oxygen is bactericidal for *Clostridium perfringens*, in addition to promoting a definitive inhibitory effect on the growth of toxins in most aerobic and microaerophilic microorganisms. The action of HBO on anaerobes is based on the production of free radicals such as superoxide, dismutase, catalase and peroxidase. More than 20 different clostridial exotoxins have been identified, and the most prevalent is alphatoxine (phospholipase C), which is haemolytic, tissue necrotizing and lethal. Other toxins, acting in synergy, promote anaemia, jaundice, renal failure, cardiotoxicity and brain dysfunction. Thetatoxine is responsible for vascular injury and consequent acceleration of tissue necrosis. HBO blocks the production of alphatoxine and thetatoxine and inhibits bacterial growth [Jain, 2004].

HBO applications in sports medicine

The healing of a sports injury has its natural recovery, and follows a fairly constant pattern irrespective of the underlying cause. Three phases have been identified in this process: the inflammatory phase, the proliferative phase and the remodelling phase. Oxygen has an important role in each of these phases [Ishii *et al.* 2005].

In the inflammatory phase, the hypoxia-induced factor-1α, which promotes, for example, the glycolytic system, vascularization and angiogenesis, has been shown to be important. However, if the oxygen supply could be controlled without promoting blood flow, the blood vessel permeability could be controlled to reduce swelling and consequently sharp pain.

In the proliferative phase, in musculoskeletal tissues (except cartilage), the oxygen supply to the injured area is gradually raised and is essential for the synthesis of extracellular matrix components such as fibronectin and proteoglycan.

In the remodelling phase, tissue is slowly replaced over many hours using the oxygen supply provided by the blood vessel already built into the organization of the musculoskeletal system, with the exception of the cartilage. If the damage is small, the tissue is recoverable with nearly perfect organization but, if the extent of the damage is large, a scar (consisting mainly of collagen) may replace tissue. Consequently, depending on the injury, this collagen will become deficiently hard or loose in the case of muscle or ligament repair, respectively.

The application of HBO for the treatment of sports injuries has recently been suggested in the scientific literature as a therapy

modality: a primary or an adjunct treatment [Babul *et al.* 2003]. Although results have proven to be promising in terms of using HBO as a treatment modality in sports-related injuries, these studies have been limited due to the small sample sizes, lack of blinding and randomization problems [Babul and Rhodes, 2000].

Even fewer studies referring to the use of HBO in high level athletes can be found in the literature. Ishii and colleagues reported the use of HBO as a recovery method for muscular fatigue during the Nagano Winter Olympics [Ishii *et al.* 2005]. In this experiment seven Olympic athletes received HBO treatment for 30–40 minutes at 1.3 ATA with a maximum of six treatments per athlete and an average of two. It was found that all athletes benefited from the HBO treatment presenting faster recovery rates. These results are concordant with those obtained by Fischer and colleagues and Haapaniemi and colleagues that suggested that lactic acid and ammonia were removed faster with HBO treatment leading to shorter recovery periods [Haapaniemi *et al.* 1995; Fischer *et al.* 1988].

Also in our experience at the Matosinhos Hyperbaric Unit several situations, namely fractures and ligament injuries, have proved to benefit from faster recovery times when HBO treatments were applied to the athletes.

Muscle injuries

Muscle injury presents a challenging problem in traumatology and commonly occurs in sports. The injury can occur as a consequence of a direct mechanical deformation (as contusions, lacerations and strains) or due to indirect causes (such as ischemia and neurological damage) [Li *et al.* 2001]. These indirect injuries can be either complete or incomplete [Petersen and Hölmich, 2005].

In sport events in the United States, the incidence of all injuries ranges from 10% to 55%. The majority of muscle injuries (more than 90%) are caused either by excessive strain or by contusions of the muscle [Järvinen *et al.* 2000]. A muscle suffers a contusion when it is subjected to a sudden, heavy compressive force, such as a direct blow. In strains, however, the muscle is subjected to an excessive tensile force leading to the overstraining of the myofibres and, consequently, to their rupture near the myotendinous junction [Järvinen *et al.* 2007].

Muscle injuries represent a continuum from mild muscle cramp to complete muscle rupture, and in between is partial strain injury and delayed onset muscle soreness (DOMS) [Petersen and Hölmich, 2005]. DOMS usually occurs following unaccustomed physical activity and is accompanied by a sensation of discomfort within the skeletal muscle experienced by the novice or elite athlete. The intensity of discomfort increases within the first 24 hours following cessation of exercise, peaks between 24 and 72 hours, subsides and eventually disappears by 5–7 days post-exercise [Cervaens and Barata, 2009].

Oriani and colleagues first suggested that HBO might accelerate the rate of recovery from injuries suffered in sports [Oriani *et al.* 1982]. However, the first clinical report appeared only in 1993 where results suggested a 55% reduction in lost days to injury, in professional soccer players in Scotland suffering from a variety of injuries following the application of HBO. These values were based on a physiotherapist's estimation of the time course for the injury *versus* the actual number of days lost with routine therapy and HBO treatment sessions [James *et al.* 1993]. Although promising, this study needed a control group and required a greater homogeneity of injuries as suggested by Babul and colleagues [Babul *et al.* 2000].

DOMS. DOMS describes a phenomenon of muscle pain, muscle soreness or muscle stiffness that is generally felt 12–48 hours after exercise, particularly at the beginning of a new exercise program, after a change in sporting activities, or after a dramatic increase in the duration or intensity of exercise.

Staples and colleagues in an animal study, used a downhill running model to induce damage, and observed significant changes in the myeloperoxidase levels in rats treated with hyperbaric oxygen compared with untreated rats [Staples *et al.* 1995]. It was suggested that hyperbaric oxygen could have an inhibitory effect on the inflammatory process or the ability to actually modulate the injury to the tissue.

In 1999, the same group conducted a randomized, controlled, double-blind, prospective study to determine whether intermittent exposures to hyperbaric oxygen enhanced recovery from DOMS of the quadriceps by using 66 untrained men between the ages of 18 and 35 years

[Staples *et al.* 1999]. After the induction of muscle soreness, the subjects were treated in a hyperbaric chamber over a 5-day period in two phases: the first phase with four groups (control, hyperbaric oxygen treatment, delayed treatment and sham treatment); and in the second phase three groups (3 days of treatment, 5 days of treatment and sham treatment). The hyperbaric exposures involved 100% oxygen for 1 hour at 2.0 ATA. The sham treatments involved 21% oxygen for 1 hour at 1.2 ATA. In phase 1, a significant difference in recovery of eccentric torque was noted in the treatment group compared with the other groups as well as in phase 2, where there was also a significant recovery of eccentric torque for the 5-day treatment group compared with the sham group, immediately after exercise and up to 96 hours after exercise. However, there was no significant difference in pain in either phase. The results suggested that treatment with hyperbaric oxygen may enhance recovery of eccentric torque of the quadriceps muscle from DOMS. This study had a complex protocol and the experimental design was not entirely clear (exclusion of some participants and the allocation of groups was not clarified), which makes interpretation difficult [Bennett *et al.* 2005a].

Mekjavic and colleagues did not find any recovery from DOMS after HBO. They studied 24 healthy male subjects who were randomly assigned to a placebo group or a HBO group after being induced with DOMS in their right elbow flexors [Mekjavic *et al.* 2000]. The HBO group was exposed to 100% oxygen at 2.5 ATA and the sham group to 8% oxygen at 2.5 ATA both for 1 hour per day and during 7 days. Over the period of 10 days there was no difference in the rate of recovery of muscle strength between the two groups or the perceived pain. Although this was a randomized, double-blind trial, this was a small study [Bennett *et al.* 2005a].

Harrison and colleagues also studied the effect of HBO in 21 healthy male volunteers after inducing DOMS in the elbow flexors [Harrison *et al.* 2001]. The subjects were assigned to three groups: control, immediate HBO and delayed HBO. These last two groups were exposed to 2.5 ATA, for 100 min with three periods of 30 min at 100% oxygen intercalated with 5 min with 20.93% oxygen between them. The first group began the treatments with HBO after 2 hours and the second group 24 hours postexercise and both were administered daily for 4 days. The delayed HBO group were also given a sham treatment with HBO at day 0 during the same time as the following days' treatments but with 20.93% oxygen at a minimal pressure. The control group had no specific therapy. There were no significant differences between groups in serum creatine kinase (CK) levels, isometric strength, swelling or pain, which suggested that HBO was not effective on DOMS. This study also presented limitations such as a small sample size and just partial blinding [Bennett *et al.* 2005a].

Webster and colleagues wanted to determine whether HBO accelerated recovery from exercise-induced muscle damage in 12 healthy male volunteers that underwent strenuous eccentric exercise of the gastrocnemius muscle [Webster *et al.* 2002]. The subjects were randomly assigned to two groups, where the first was the sham group who received HBO with atmospheric air at 1.3 ATA, and the second with 100% oxygen with 2.5 ATA, both for 60 minutes. The first treatment was 3–4 hours after damage followed by treatments after 24 and 48 hours. There was little evidence in the recovery measured data, highlighting a faster recovery in the HBO group in the isometric torque, pain sensation and unpleasantness. However, it was a small study with multiple outcomes and some data were not used due to difficulties in interpretation [Bennett *et al.* 2005a].

Babul and colleagues also conducted a randomized, double-blind study in order to find out whether HBO accelerated the rate of recovery from DOMS in the quadriceps muscle [Babul *et al.* 2003]. This exercise-induced injury was produced in 16 sedentary female students that were assigned into two groups: control and HBO. The first was submitted to 21% oxygen at 1.2 ATA, and the second to 100% oxygen at 2.0 ATA for 60 minutes at 4, 24, 48 and 72 hours postinjury. There were no significant differences between the groups in the measured outcomes. However, this was also a small study with multiple outcomes, with a complex experimental design with two distinct phases with somewhat different therapy arms [Bennett *et al.* 2005a].

Germain and colleagues had the same objective as the previous study but this time the sample had 10 female and 6 male subjects that were randomly assigned into two groups [Germain *et al.* 2003]: the control group that did not undergo

any treatment and the HBO group that was exposed to 95% oxygen at 2.5 ATA during 100 minutes for five sessions. There were no significant differences between the groups which lead to the conclusion that HBO did not accelerate the rate of recovery of DOMS in the quadriceps. Once again, this was a very small and unblinded study that presented multiple outcomes [Bennett *et al.* 2005a].

Muscle stretch injury. In 1998, Best and colleagues wanted to analyse whether HBO improved functional and morphologic recovery after a controlled induced muscle stretch in the *tibialis anterior* muscle–tendon unit [Best *et al.* 1998]. They used a rabbit model of injury and the treatment group was submitted to a 5-day treatment with 95% oxygen at 2.5 ATA for 60 minutes. Then, after 7 days, this group was compared with a control group that did not undergo HBO treatment. The results suggested that HBO administration may play a role in accelerating recovery after acute muscle stretch injury.

Ischemia. Another muscle injury that is often a consequence of trauma is ischemia. Normally it is accompanied by anaerobic glycolysis, the formation of lactate and depletion of high-energy phosphates within the extracellular fluid of the affected skeletal muscle tissue. When ischemia is prolonged it can result in loss of cellular homeostasis, disruption of ion gradients and breakdown of membrane phospholipids. The activation of neutrophils, the production of oxygen radicals and the release of vasoactive factors, during reperfusion, may cause further damage to local and remote tissues. However, the mechanisms of ischemia–reperfusion-induced muscle injury are not fully understood [Bosco *et al.* 2007]. These authors aimed to see the effects of HBO in the skeletal muscle of rats after ischemia-induced injury and found that HBO treatment attenuated significantly the increase of lactate and glycerol levels caused by ischemia, without affecting glucose concentration, and modulating antioxidant enzyme activity in the postischemic skeletal muscle.

A similar study was performed in 1996 [Haapaniemi *et al.* 1996] in which the authors concluded that HBO had positive aspects for at least 48 hours after severe injury, by raising the levels of high-energy phosphate compounds, which indicated a stimulation of aerobic oxidation in the mitochondria. This maintains the transport of ions and molecules across the cell membrane and optimizes the possibility of preserving the muscle cell structure.

Gregorevic and colleagues induced muscle degeneration in rats in order to see whether HBO hastens the functional recovery and myofiber regeneration of the skeletal muscle [Gregorevic *et al.* 2000]. The results of this study demonstrated that the mechanism of improved functional capacity is not associated with the reestablishment of a previously compromised blood supply or with the repair of associated nerve components, as seen in ischemia, but with the pressure of oxygen inspired with a crucial role in improving the maximum force-producing capacity of the regenerating muscle fibres after this myotoxic injury. In addition, there were better results following 14 days of HBO treatment at 3 ATA than at 2 ATA.

Ankle sprains

In 1995 a study conducted at the Temple University suggested that patients treated with HBO returned approximately 30% faster than the control group after ankle sprain. The authors stated, however, that there was a large variability in this study design due to the difficulty in quantifying the severity of sprains [Staples and Clement, 1996].

Interestingly, Borromeo and colleagues, in a randomized, double-blinded study, observed in 32 patients who had acute ankle sprains the effects of HBO in its rehabilitation [Borromeo *et al.* 1997]. The HBO group was submitted to 100% oxygen at 2 ATA for 90 minutes for the first session and 60 minutes for the other two. The placebo group was exposed to ambient air, at 1.1 ATA for 90 minutes, both groups for three sessions over 7 days. The HBO group had an improvement in joint function. However, there were no significant differences between groups in the subjective pain, oedema, passive or active range of motion or time to recovery. This study included an average delay of 34 hours from the time of injury to treatment, and it had short treatment duration [Bennett *et al.* 2005a].

Medical collateral ligament

Horn and colleagues in an animal study surgically lacerated medial collateral ligament of 48 rats [Horn *et al.* 1999]. Half were controls without intervention and the other half were exposed to HBO at 2.8 ATA for 1.5 hours

a day over 5 days. Six rats from each group were euthanized at 2, 4, 6 and 8 weeks and at 4 weeks a statistically greater force was required to cause failure of the previously divided ligaments for those exposed to HBO than in the control group. After 4 weeks, an interesting contribution from HBO could be seen in that it promoted the return of normal stiffness of the ligament.

Ishii and colleagues induced ligament lacerations in the right limb of 44 rats and divided them into four groups [Ishii *et al.* 2002]: control group, where animals breathed room air at 1 ATA for 60 min; HBO treatment at 1.5 ATA for 30 min once a day; HBO treatment at 2 ATA for 30 min once a day; and 2 ATA for 60 min once a day. After 14 days postinjury, of the three exposures the last group was more effective in promoting healing by enhancing extracellular matrix deposition as measured by collagen synthesis.

Mashitori and colleagues removed a 2-mm segment of the medial collateral ligament in 76 rats [Mashitori *et al.* 2004]. Half of these rats were exposed to HBO at 2.5 ATA for 2 hours for 5 days per week and the remaining rats were exposed to room air. The authors observed that HBO promotes scar tissue formation by increasing type I procollagen gene expression, at 7 and 14 days after the injury, which contribute for the improvement of their tensile properties.

In a randomized, controlled and double-blind study, Soolsma examined the effect of HBO at the recovery of a grade II medial ligament of the knee presented in patients within 72 hours of injury. After one group was exposed to HBO at 2 ATA for 1 hour and the control group at 1.2 ATA, room air, for 1 hour, both groups for 10 sessions, the data suggested that, at 6 weeks, HBO had positive effects on pain and functional outcomes, such as decreased volume of oedema, a better range of motion and maximum flexion improvement, compared with the sham group [Soolsma, 1996].

Anterior cruciate ligament

Yeh and colleagues used an animal model to investigate the effects of HBO on neovascularization at the tendon–bone junction, collagen fibres of the tendon graft and the tendon graft–bony interface which is incorporated into the osseous tunnel [Yeh *et al.* 2007]. The authors used 40 rabbits that were divided into two groups: the control group that was maintained in cages at normal air and the HBO group that was exposed to 100% oxygen at 2.5 ATA for 2 hours, for 5 days. The authors found that the HBO group had significantly increased the amount of trabecular bone around the tendon graft, increasing its incorporation to the bone and therefore increasing the tensile loading strength of the tendon graft. They assumed that HBO contributes to the angiogenesis of blood vessels, improving the blood supply which leads to the observed outcomes.

Takeyama and colleagues studied the effects of HBO on gene expressions of procollagen and tissue inhibitor of metalloproteinase (TIMPS) in injured anterior cruciate ligaments [Takeyama *et al.* 2007]. After surgical injury animals were divided into a control group and a group that was submitted to HBO, 2.5 ATA for 2 hours, for 5 days. It was found that even though none of the lacerated anterior cruciate ligaments (ACLs) united macroscopically, there was an increase of the gene expression of type I procollagen and of TIMPS 1 and 2 for the group treated with HBO. These results indicate that HBO enhances structural protein synthesis and inhibits degradative processes. Consequently using HBO as an adjunctive therapy after primary repair of the injured ACL is likely to increase success, a situation that is confirmed by the British Medical Journal Evidence Center [Minhas, 2010].

Fractures

Classical treatment with osteosynthesis and bone grafting is not always successful and the attempt to heal nonunion and complicated fractures, where the likelihood of infection is increased, is a challenge.

A Cochrane review [Bennett *et al.* 2005b] stated that there is not sufficient evidence to support hyperbaric oxygenation for the treatment of promoting fracture healing or nonunion fracture as no randomized evidence was found. During the last 10 years this issue has not been the subject of many studies.

Okubo and colleagues studied a rat model in which recombinant human bone morphogenetic protein-2 was implanted in the form of lyophilized discs, the influence of HBO [Okubo *et al.* 2001]. The group treated with HBO, exposed to 2 ATA for 60 min daily, had significantly increased new bone formation compared with

the control group and the cartilage was present at the outer edge of the implanted material after 7 days.

Komurcu and colleagues reviewed retrospectively 14 cases of infected tibial nonunion that were treated successfully [Komurcu *et al.* 2002]. Management included aggressive debridement and correction of defects by corticotomy and internal bone transport. The infection occurred in two patients after the operation which was successfully resolved after 20–30 sessions of HBO.

Muhonen and colleagues aimed to study, in a rabbit mandibular distraction osteogenesis model, the osteogenic and angiogenic response to irradiation and HBO [Muhonen *et al.* 2004]. One group was exposed to 18 sessions of HBO until the operation that was performed 1 month after irradiation. The second group did not receive HBO and the controls underwent surgery receiving neither irradiation nor HBO. The authors concluded that previous irradiation suppresses osteoblastic activity and HBO changes the pattern of bone-forming activity towards that of nonirradiated bone.

Wang and colleagues, in a rabbit model, were able to demonstrate that distraction segments of animals treated with HBO had increased bone mineral density and superior mechanical properties comparing to the controls and yields better results when applied during the early stage of the tibial healing process [Wang *et al.* 2005].

Conclusion

In the various studies, the location of the injury seemed to have an influence on the effectiveness of treatment. After being exposed to HBO, for example, injuries at the muscle belly seem to have less benefit than areas of reduced perfusion such as muscle–tendon junctions and ligaments.

With regards to HBO treatment, it is still necessary to determine the optimal conditions for these orthopaedic indications, such as the atmosphere pressure, the duration of sessions, the frequency of sessions and the duration of treatment. Differences in the magnitude of the injury and in the time between injury and treatment may also affect outcomes.

Injuries studies involving bones, muscles and ligaments with HBO treatment seem promising. However, they are comparatively scarce and the quality of evidence for the efficacy of HBO is low. Orthopaedic indications for HBO will become better defined with perfection of the techniques for direct measurement of tissue oxygen tensions and intramuscular compartment pressures. Despite evidence of interesting results when treating high-performance athletes, these treatments are multifactorial and are rarely published. Therefore, there is a need for larger samples, randomized, controlled, double-blind clinical trials of human (mainly athletes) and animal models in order to identify its effects and mechanisms to determine whether it is a safe and effective therapy for sports injuries treatments.

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Conflict of interest statement

None declared.

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