Hyperbaric Oxygen Therapy in Sports Musculoskeletal Injuries

NAVID MOGHADAM[1], MICHINARI HIEDA[2,3], LINDSAY RAMEY[3], BENJAMIN D. LEVINE[2,3], and RENIE GUILLIOD[2,3]

[1]Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, IRAN; [2]Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, TX; and [3]The University of Texas Southwestern Medical Center, Dallas, TX

ABSTRACT

MOGHADAM, N., M. HIEDA, L. RAMEY, B. D. LEVINE, and R. GUILLIOD. Hyperbaric Oxygen Therapy in Sports Musculoskeletal Injuries. *Med. Sci. Sports Exerc.*, Vol. 52, No. 6, pp. 1420–1426, 2020. Hyperbaric oxygen therapy (HBOT) is a well-established treatment for a variety of conditions. Hyperbaric oxygen therapy is the administration of 100% oxygen breathing in a pressure vessel at higher than atmospheric pressure (1 atmosphere absolute = 101 kPa). Typically, treatment is given daily for between 1 and 2 h at pressures of 2.0 to 2.8 ATA, depending on the indication. Sporting injuries are often treated over 3 to 10 sessions. Hyperbaric oxygen therapy has been documented to be effective and is approved in 14 medical indications by the Undersea and Hyperbaric Medical Society, including, but not limited to, carbon monoxide poisoning, compromised skin grafts and flaps, crush injuries, necrotizing soft tissue infections, and nonhealing ulcers with arterial insufficiencies. Recently, HBOT for sports musculoskeletal injuries is receiving increased attention. Hyperbaric oxygen therapy may allow injured athletes to recover faster than normal rehabilitation methods. Any reduction in collegiate and professional athletes' rehabilitation period can be financially significant for top-level sports teams; however, further research is required to confirm HBOT's benefits on sports musculoskeletal injuries. The purpose of this review to discuss the current understanding of HBOT as a treatment modality for common musculoskeletal injuries in sport medicine. Moreover, we will highlight the advantages and disadvantages of this modality, as well as relevant clinical and research applications. **Key Words:** HYPERBARIC OXYGEN THERAPY, SPORTS MUSCULOSKELETAL INJURIES, THERAPY, REHABILITATION

INDICATIONS AND GENERAL PROTOCOLS OF HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy (HBOT) refers to the administration of pure oxygen intermittently at a pressure higher than 1 atmosphere absolute (ATA) in a hyperbaric chamber. For clinical purposes, the Undersea and Hyperbaric Medical Society (UHMS) indicates that pressurization should be 1.4 ATA (141.86 kPa) or higher to be effective. The common range of pressure used is between 2 and 2.8 ATA. (1) Typically, each session takes between 60 and 120 min. Treatment can be carried out in either a monoplace or multiplace chamber. The former accommodates a single patient where the entire chamber is usually pressurized with 100% oxygen, and the patient breathes the ambient chamber oxygen directly. The latter holds two or more people (patients, observers, and/or support personnel), and the chamber is pressurized with compressed air while the patients breathe near 100% oxygen via masks, head hoods, or endotracheal tubes. (1–3) Hyperbaric oxygen therapy has been used in a wide variety of medical settings. (4) In the United States, the Food and Drug Administration defers to the UHMS to establish the list of indications for which HBOT has sufficient evidence to support its use. Currently, 14 medical indications have been approved However in other countries a larger number of indications are recognized (Table 1) (1). The European Committee for Hyperbaric Medicine has accepted 30 indications for HBOT. These indications are divided in three categories, European Committee for Hyperbaric Medicine type 1 to 3: type 1, where HBOT is strongly indicated as a primary treatment method and its use is supported by sufficiently strong evidence. Type 2, where HBOT is suggested and its use is supported by acceptable levels of evidence. Type 3, where HBOT can be considered as a possible/optional measure, but it is not yet supported by sufficiently strong evidence (5) The branch of Hyperbaric Oxygen Medicine of the Chinese Medical Association endorses 12 emergency indications and 48 nonemergency indications (6).

POTENTIAL MECHANISMS AND PHYSIOLOGICAL EFFECTS OF HBOT

Hyperbaric oxygen therapy in the short-term enhances oxygen delivery with vasoconstriction, which reduces edema, improves neutrophil phagocytic function that mitigates infection, has anti-inflammatory effects, and mitigates ischemia–reperfusion injury. Over longer periods and with repeat administration, HBOT

Address for correspondence: Renie Guilliod, M.D., Institute for Exercise and Environmental Medicine, Suite 435, 7232 Greenville Ave, Dallas, TX 75231; E-mail: RenieGuilliod@texashealth.org.
Submitted for publication July 2019.
Accepted for publication December 2019.

0195-9131/20/5206-1420/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000002257

TABLE 1. Therapeutic uses of hyperbaric oxygen according to UHMS.

1. Air or gas embolism
2. Carbon monoxide poisoning/carbon monoxide poisoning complicated by cyanide poisoning
3. Clostridial myositis and myonecrosis (gas gangrene)
4. Crush injuries, compartment syndrome and other traumatic ischemias
5. Decompression sickness
6. Arterial Insufficiencies
   (a) Central retinal artery occlusions
   (b) Selected problem wounds—diabetic ulcers (microvascular insufficiency)
7. Severe anemia
8. Intracranial abscesses
9. Necrotizing infections
10. Osteomyelitis (refractory)
11. Delayed radiation injury (soft tissue and bony necrosis)
12. Compromised grafts and flaps
13. Acute thermal burn injury
14. Idiopathic sudden sensorineural hearing loss

The UHMS approves use of hyperbaric oxygen for a few conditions for which there is thought to be reasonable scientific evidence or well validated clinical experience (1).

induces neovascularization and neoangiogenesis as well as stimulation of collagen production by fibroblasts. (7) All of these effects could enhance the rehabilitation of an injured muscle in the inflammatory and proliferative phases of recovery.

The plasma oxygen concentration is normally approximately 3 $mL \cdot L^{-1}$ at sea level (8). Despite the varying need for oxygenation between different tissues, typical resting tissues need about 60 mL of $oxygen \cdot L^{-1}$ to maintain normal metabolism; dissolved oxygen levels can reach this level (60 $mL \cdot L^{-1}$ plasma), without considering hemoglobin bound oxygen at a pressure of 3 ATA (304 kPa) (4). During carbon monoxide poisoning or in severe anemia without the possibility of transfusion, this mechanism can help deliver oxygen without the need for transfer via hemoglobin. Delivering oxygen at 300 kPa leads to achieving 270 kPa (2025 mm Hg) of oxygen in the arterial blood and roughly 53 kPa (~400 mm Hg) in the tissues (4,9).

The most important effect of HBOT, beyond offering more O_2 to the tissues, is producing free radicals in a therapeutic range for cell signaling. Hyperbaric oxygen therapy induces oxidative stress by mean of controlled production of reactive oxygen and nitrogen species, which causes the activation of cellular processes and pathways (7,10–12). Some of the most relevant mechanisms are as follows: increased growth factors (e.g., hypoxia-inducible factor 1-α) (13), vascular endothelial growth factor (14,15), stromal-derived factor 1 (13), mobilization of bone marrow-derived stem cells (CD34) (7), and the reduction of neutrophil adhesion (modification of integrin β-2) that mitigates ischemia-reperfusion injury (7,16).

ADVERSE EFFECTS OF HBOT

Hyperbaric oxygen therapy is mostly safe, and the adverse effects are mainly mild and reversible. There are two main concerns using HBOT, (A) barotrauma (trauma caused by pressure) and (B) oxygen toxicity (17).

Barotrauma is caused by an inability to balance pressure between the pressurized environment and any gas-filled space in the body. The middle ear is the most commonly affected place of barotrauma, which starts with tympanic membrane hyperemia and can lead to a tympanic membrane rupture. Air trapping in sinuses due to obstruction by a polyp or inflammation can also lead to increased susceptibility to barotrauma. Any air pocket in teeth due to dental decay can lead to a large amount of pain. An important but rare consideration is barotrauma to the lungs during depressurization at the end of the HBOT. This represents a risk if the patient holds the breath or has a lung condition with air trapping in the airways, which can lead to pneumomediastinum, pneumothorax, or gas embolism.

Oxygen toxicity is a condition resulting from the harmful effects of breathing oxygen at increased partial pressures (18,19). As noted above, at least some of the beneficial effects of HBOT may be through controlled oxidative stress. Antioxidant defenses are generally adequate during the hyperoxic exposure created by typical clinical HBOT. Nonetheless, there may be negative aspects to high levels of oxygen radicals and oxygen toxicity in the central nervous system (CNS) can occur (17). The CNS oxygen toxicity manifests as symptoms such as visual changes, ringing in the ears, nausea, twitching, anxiety, confusion, and dizziness. The CNS oxygen toxicity during clinical hyperbaric oxygen treatment is an oxygen toxicity seizure (17). Pulmonary oxygen toxicity (POT) is caused by exposure of the lungs to oxygen. Although described after prolonged normobaric exposures to concentrations above 50%, the development of POT manifestations is much more rapid with hyperbaric exposure. Pulmonary oxygen toxicity is characterized by acute exudative manifestations including edema, hemorrhage and cell destruction, and subacute proliferative manifestations including fibrosis and hyperplasia. Clinically important POT is highly unusual in association with routine doses of HBOT, but can occur with prolonged exposures (17).

HBOT FOR SPORTS MUSCULOSKELETAL INJURIES

Hyperbaric oxygen therapy has become popular among injured athletes because of its hypothetical benefits on accelerated recovery, especially among professional athletes or those with substantial financial resources. However, despite the widespread popular appeal, the evidence supporting this practice is meager. Previous reviews have investigated the possible role of HBOT in specific injuries or sports injuries in general (2,3,20–22), but there has not been any new review since 2005.

MUSCLE INJURY AND HBOT

Muscle injuries encompass a broad range of pathologies, including muscle cramps, delayed-onset muscle soreness (DOMS), muscle contusion and muscle tears (23). Muscle tears (often referred to as muscle strains) are one of the most common musculoskeletal injuries and can account for prolonged time missed from sport. In a recent study of injuries among national collegiate athletes from 2009 to 2015, muscle strains were found to be the second most common diagnosis that resulted in missed participation for more than 21 d (24). Although historically classified into three grades based on severity of symptoms and degree of tear, ranging from small partial tear to complete rupture, a number of new classification systems have been

proposed. Currently, there is little consensus on a comprehensive and evidenced based system to classify muscle injuries (25). Delayed-onset muscle soreness is characterized by discomfort in skeletal muscles after more than usual intensity exercise; it peaks in 24 to 48 h after the exercise and is typically resolved in 5 to 7 d. This muscle damage can lead to a transient decline in physical performance (26) and/or increased risk of injury (27). The ability for sports physicians to reduce the recovery period after muscle injuries is extremely significant, especially in the realm of financial incentives in professional sports where slightly faster return to play is of most importance in the light of economy of professional sports. The team has to continue paying the salary of injured athlete despite the fact that he or she is not playing; as an example, the cost of salaries for injured players on the disabled list of Major League Baseball was over US $1.6 billion in 2013 to 2015 (28). This demand for faster return to service is also the case in military settings (29).

Few clinical studies have suggested an advantage of HBOT for sports injuries over routine care, especially DOMS (see Table 2).

TABLE 2. Summary of human clinical trials for HBOT in sports related injuries.

Reference	Injury Type	Groups	Intervention	Summary of Results (Effect of HBOT in Compare to the Control)
Soolsma, 1996 (54)	Grade II MCL injury	HBOT group *n* = 7	10 sessions of 2.5 ATA 100% O_2	↓volume of edema ↓muscle wasting
		Control Group *n* = 7	10 sessions of 1.2 ATA air	↑range of motion ↑Maximum flexion ↔ Severity of pain ↔ One legged jump test
Borromeo et al., 1997 (31)	Ankle sprain within 72 h	HBOT group *n* = 16	3 sessions 2 ATA 100% O_2	↑functional index improvement* ↔ reduced swelling
		control group *n* = 16	3 sessions 1.1 ATA air	↔ pain ↔ range of motion ↔ time to recovery
Staples et al., 1999 (32)	Induced DOMS of quadriceps		Phase 1	Phase 1
		HBO group *n* = 9	3 sessions 2.5 ATA 100% O_2 and 2 sessions 1.2 ATA 21% O_2 after that	↔ Pain score ↑Recovery of torque (HBO vs Delayed HBO, Sham, and control)*
		Delayed HBO group *n* = 9	2 sessions 1.2 ATA 21% O_2 and 3 sessions 2.5 ATA 100% O_2 after that	Phase 2
		Sham group *n* = 9	5 sessions 1.2 ATA 21% O_2	↔ Pain score ↑Mean eccentric quadriceps torque (5 d HBO vs Sham and 3 d HBO)*
		Control group *n* = 9	No treatment	
			Phase 2	
		3 d HBO group *n* = 10	3 sessions 2.5 ATA 100% O_2	
		5 d HBO group *n* = 10	5 sessions 2.5 ATA 100% O_2	
		Sham group *n* = 10	5 sessions 1.2 ATA 21% O_2	
Mekjavic et al., 2000 (33)	Induced DOMS of elbow flexors	HBOT groups *n* = 12	7 sessions 2.5 ATA 100% O_2 (PIO_2 = 2.5 ATA)	↔ the rate of recovery ↔ muscle strength
		Control groups *n* = 12	7 sessions 2.5 ATA normoxic (PIO_2 = 0.2 ATA)	↔ peaked Perceived soreness ↔ increases in arm circumference
Harrison et al., 2001 (34)	Exercise-induced muscle injury with Preacher Curl	Immediate HBOT *n* = 6	5 sessions 2.5 ATA 100% O_2 (starting day 0)	↔ cross-sectional area ↔ T2 relaxation time in MRI
		Delayed HBOT *n* = 7	4 sessions 2.5 ATA 100% O_2 (starting day 1)	↔ isometric strength serum CK level ↔ perceived soreness
		Control group *n* = 7	No treatment	
Webster et al., 2002 (35)	Exercise-induced muscle injury in gastrocnemius	HBOT group *n* = 6	3 sessions of 2.5 ATA 100% O_2	↑isometric peak torque recovery* ↓pain perception*
		Control group *n* = 6	3 sessions of 1.3 ATA air	↔ isokinetic peak torque ↔ muscular endurance ↔ T2 relaxation time in MRI ↔ cross-sectional area
Babul et al., 2003 (36)	Induced DOMS of knee flexors	HBOT group *n* = 8	5 sessions of 2.0 ATA 100% O_2	↔ Pain ↔ Strength
		control group *n* = 8	5 sessions of 1.2 ATA air	↔ quadriceps circumference ↔ creatine kinase ↔ malondialdehyde ↔ MRI images (T2 and STIR)
Germain et al., 2003 (37)	Induced DOMS of quadriceps femoris	HBOT group *n* = 8	5 sessions of 2.5 ATA 95% O_2	↔ creatine kinase ↔ muscle soreness
		Control group *n* = 8	No treatment	↔ leg circumference ↔ isokinetic peak torque

*Statistically significant ($P < 0.05$) difference between HBOT and control group in that outcome.
↑Outcome variable is higher in HBOT group in compare to control group.
↓Outcome variable is lower in HBOT group in compare to control group.
↔The outcome variable is similar in HBOT and control group.

Potential Mechanism of HBOT for Muscle Injury in Acute and Proliferative Phases

Acute phase. Inflammation after muscle injury includes the production and release of inflammatory cytokines, increased vascular permeability, migration of neutrophils, and edema (38). Edema increases the diffusion distance for oxygen while at the same time, increases in extracellular pressure can reduce perfusion, a combination that can result in significant hypoxia and necrosis (39). Delivering oxygen by HBOT without an increase in vascular dilation and permeability can hypothetically simultaneously reduce edema and hypoxia. Under the effect of HBOT, the transition from an inflammatory state to a proliferative state is accelerated. This accelerated transition has been evidenced through the increase in the number of anti-inflammatory M2 macrophages (M2) in comparison to pro-inflammatory M1 macrophages (M1) in the study of Oyaizu et al (40). It has been shown that HBOT accelerates the differentiation of migrated M1 macrophages to M2 macrophages in the initial phase of healing period (40,41).

Proliferative phase. Satellite cells play a vital role in the proliferative phase of muscle rehabilitation after the injury (42). Satellite cells can undergo transformation to myoblast lineage to initiate muscle regeneration (43). Previous studies have shown that HBOT promotes a higher number of proliferating, differentiating, and quiescent satellite cells which will be reserved for the next injury (40,43). One of the important conclusions of Oyaizu and colleagues' study (40) is that HBOT accelerated regeneration processes, including satellite cell proliferation (resident stem cells) with improved muscle fiber regeneration and strength. Chaillou et al. (42) showed that the myogenic activity of satellite cells can be compromised in the hypoxic environment. Macrophages, neutrophils, and satellite cells in injured muscles release interleukin-6 (IL-6); IL-6 is involved in the IL-6/STAT3 pathway that increases the expression of the genes needed for the proliferation of satellite cells and differentiation to myoblast lineages (40). A study of HBOT in animal models showed earlier activation of the IL-6/STAT3 pathway compared with their cohorts in the control group (40). In conclusion, the *in vitro* studies suggest that HBOT can accelerate the needed proliferation and differentiation of proliferative phase.

Delayed-Onset Muscle Soreness

Staples et al. (32) demonstrated the effects of HBO on the faster recovery of DOMS in athletes for the first time, but several subsequent studies have shown inconsistent results (21,34,36,37) (see Table 2). In their systematic review, Bennett et al. (2) demonstrated higher pain scores at 48 and 72 h in the HBOT group and no differences in longer-term pain, or swelling or muscle strength at any time. There have been no further published randomized studies since that review.

Webster et al. (35) showed that HBOT led to decreased pain and increased torque and recovery in DOMS subjects with a sample size of 12 patients (six HBOT and six control groups). Mekjavic et al. (33) has been the only study which has incorporated completely similar controls with the intervention group in terms of pressure (2.5 ATA normoxic, PIO2 = 0.2 ATA); the placebo in other studies was pressurized ambient air with lower pressure than the intervention group. Using lower fraction oxygen controls to achieve an FiO_2 of 0.2 as in Webster et al. can be controversial due to the increased risk of decompression illness and other concerns about possible (untested) therapeutic effects of pressure itself or the increased pressure of N2 (44). We have discussed the concerns about the placebo pressure later in Performance bias section.

Muscle Strain and/or Contusion

We could not find any human clinical studies about using HBOT for athletes with muscle strain and/or contusion.

Cervaens Costa Maia et al. (45) showed that HBOT-exposed rats had lower creatinine kinase level, a marker of muscle damage compared with a control group in a rat model of muscle contusion. They also measured the weight of the injured muscle 72 h after injury and showed that the HBOT group had higher muscle weight in comparison to the control group. This finding should be interpreted with caution, however, because of other studies that have used muscle weight as a marker of inflammation and have shown lower muscle weight in HBOT groups (40). Best et al. used a rabbit animal model of tibialis anterior injury in 1998. They showed a significant difference in isometric torque deficit of injured muscle between the HBOT and control groups. Best et al. (46) suggested that five sessions of HBOT 24 h after the muscle-tendon unit injury can lead to better morphologic healing in the HBOT group as well as better isometric torque results. The number of new *in vitro* and animal studies and the need for guidance in future studies required us to reevaluate the current literature, search for gaps in the current literature, and offer suggestions for future studies (47).

Ligament and Tendon Injuries

Horn et al. (48) have reported that higher destructive force is needed before reaching failure in the medial collateral ligament (MCL) of rats treated with HBOT compared with a control group after induction of ligament tear and surgery; however, this difference was only apparent 4 wk after the injury and they could not find any difference after 6 wk. Ishii et al. (49) showed a dose–response relationship between the concentration and pressure of oxygen in HBOT and its effect on the healing process of ligament healing in rats. They reported that HBOT at 2 ATA was the most effective at enhancing collagen synthesis in the extracellular matrix.

The expression of matrix metalloproteinases (MMP) and type I procollagen are indicators of the beginning of the proliferation phase in the process of ligament healing (30). Takeyama et al. (30) studied using HBOT in the healing of MCL and anterior cruciate ligaments (ACL) in rats after laceration. Both ACL and MCL in the HBOT group showed significantly greater gene expression of type I procollagen and no change in type III procollagen gene expression compared with the

control group. Although MCL in the HBOT group showed macroscopic healing by scar tissue formation, none of the severed ACL united physically despite the administration of HBOT. This finding can be attributed to the intraarticular location of the ACL (avascularity) in contrast to extraarticular of the MCL. The MMP gene expression was higher in MCL in the HBOT group compared with the MCL in the control group. The expression of tissue inhibitors of metalloproteinases was higher in ACL in the HBOT group compared with ACL in the control group. Although Takeyama et al. studied the effectiveness of HBOT on ACL lacerations without any other intervention, Yeh et al. (50) used HBOT as an adjunct therapy to ACL tendon graft. They reported increased neovascularization and enhanced incorporation between tendon grafts and bone in the HBOT group. They also showed that tendon grafts have higher maximal pullout strength in the HBOT group. Chan et al. (51) designed a four-arm study to test HBOT and platelet-derived growth factor-BB's (PDGF-BB) effect on cultured cells in rabbit MCL; HBOT and HBOT plus PDGF-BB groups showed a decrease in type III collagen/type I collagen content ratio, which can lead to mechanically stronger collagen fibrils. Hsu et al. (52) used HBOT in rabbits suffering from patellar tendinopathy, which was induced by collagenase; tendons in the HBOT group showed 34.8% greater ultimate tensile load compared with the control group. Finally, and perhaps more concerningly, Mashitori et al. (53) reported a higher amount of scar tissue and type I procollagen gene expression in the injured MCL of the rats in a HBOT, compared with the control group. Only two randomized, controlled, human trials using HBOT in ligament injuries (MCL and ankle sprain) have been reported to date. Both were small, had methodological problems, and were inconclusive (31,54). Basic and animal studies have justified moving on and designing human studies to investigate the clinical effectiveness of using HBOT in ligament and tendon-injured athletes.

LIMITATIONS OF CURRENT HUMAN STUDIES

Selection bias. We cannot reject the possibility of baseline differences between groups, especially when the subjects are recruited after injury and the investigator has no prior data. Soolsma et al. (54) (HBOT for MCL injury) did not report the baseline data after the outcome measures in the groups. Borromeo et al. (31) (HBOT for ankle sprain) did report baseline measurement and there were significant differences between the groups regarding initial pain and edema (worse in HBOT group); however, the time from injury to first HBOT and the range of motion and ankle function (main outcome) were uniform. Among DOMS studies, Staples et al. (32) did not report any statistical test for investigating baseline differences between groups, they just have shown the baseline date in the raw data manner in figures; it should be mentioned that HBOT groups had higher baseline eccentric torque forces than other groups according to the reported figures in their study. Mekjavic et al. (33) also did not conduct baseline measurements in HBOT and control groups. Harrison et al. (34) reported no difference between HBOT and control groups in isometric strength but did not report any test for evaluation of baseline cross-sectional area, T2 relaxation time and serum creatinine kinase. Webster et al. (35) did not report baseline values and only reported outcomes as percentage change from nondisclosed baselines, except for the cross-sectional area, which they did reported baselines for and emphasized no significant differences between groups. It is important to mention that Webster et al. is the only study that could reproduce the findings of Staples et al. about HBOT's effectiveness in treating DOMS. Babul et al. (36) reported a 95% confidence interval of zero mean difference between control and HBOT groups and included all baseline measurements. Germain et al. (37) reported baseline values in figures and tables without mentioning any statistical test for checking baseline difference between groups. We have to emphasize the importance of reporting baseline characteristics of intervention and control groups in future studies. We can use less intimidating tests like isometric muscle strength testing, which can be conducted even with injured athletes.

Performance bias. The only human trial which used the same pressure in the chamber for both HBOT and control groups was Mekjavic et al. (33); Soolsma et al. (51), Borromeo et al. (31), Staples et al. (32), Webster et al. (35), and Babul et al. (36) used 1.1, 1.2, or 1.3 ATA of pressure as sham. There are some concerns that this last type of sham is less effective in blinding than a controls intervention with the same pressure with HBOT but with hypoxic mixture to mimic normoxic conditions (PIO_2 = 0.2 ATA). However, Weaver et al. (55) ran a prospective study to test if the divers or other people familiar with hyperbaric situation can discern chamber pressure (1.5 ATA 100% oxygen vs 1.2 ATA ambient air). They showed that experienced divers could not discriminate chamber pressures of 1.5 ATA and 1.2 ATA. but they did not reach 2.0 or 2.5 ATA which are the most common protocols. Clarke (56) reported that recreational SCUBA divers could not differentiate between 2.0 ATA 100% oxygen and 1.1 to 1.3 ATA ambient air protocols. However, it did not report in detail how they evaluated the effect of learning on repeated exposures. A narrative review by Lansdrop and van Hulst (57) in 2018 concluded that the best placebo is using air with a lower pressure than the HBOT group. In the authors' opinion, however, there are still two theoretical concerns with this approach:

1. It is not possible to simultaneously treat subjects of the study group with subjects of the control group nor is it possible to have patients under treatment pressure and study subjects of the control group at the same time (which means they cannot be treated exactly the same). With the placebo approach using the same treatment pressure (2 ATA, for example) breathing a hypoxic mixture (10.5% oxygen and 89.5% nitrogen), patients and study subjects of both groups (control and study) can be treated in the chamber at the same time, completely blinded.

2. In the vast majority of multiplace hyperbaric chambers, it is not possible to obtain an appropriate door seal until the internal pressure reaches at least 1.2 ATA. Without enough pressure to obtain the proper seal, a characteristic noise is produced that would inform the study subjects, and the personnel inside and outside the chamber, that there is little pressure inside the chamber.

We should also mention that control groups did not receive any treatment in Harrison et al. (34) and Germain et al. (37) studies.

Detection bias. Half of the eight human trials have used blinded assessor for the outcome measurements (Table 2), three of eight studies did not mention if the assessors of the outcomes measure were blinded and Webster et al. (35) specified that their study was single blinded.

FUTURE STRATEGIES TO BRIDGE THE KNOWLEDGE GAP

We suggest that future studies use larger sample sizes or matching to avoid differences in the baseline of HBOT and control groups. They could report baseline data if there is no difference in the baseline measures of outcome measures. Blindness strategy is another concern in future study designs, and the aforementioned concerns about the blindness should be addressed. The blindness of the investigator, who is responsible for the assessment of outcome measures, can attenuate substantial bias.

All the current human trials have mentioned randomization in their design, but considering the limited number of participants, randomization might not be enough for attenuating allocation bias. We suggest that future studies use large pools of injured athletes with different injuries but with stratification and matching. They can use relative outcomes (healing time of any specific injury in HBOT group/healing time of the same injury in control group) as an outcome measure, which enables them to use a pool of injured athletes with different injuries.

Despite the number of basic and animal studies using HBOT in conditions other than muscle soreness, human trial studies are scarce. Designing new human studies for evaluation of the effectiveness of HBOT on muscle strains, contusion, tendon, and ligament injuries should be the next step in the light of recent *in vitro* and animal studies.

CONCLUSIONS

Hyperbaric oxygen therapy has the special capacity to enhance oxygen delivery, reduce edema and pathologic inflammation, mitigate ischemia/reperfusion injury, improve collagen synthesis and deposition, and induce neovascularization and neoangiogenesis. These underlying mechanisms have the potential to help the process of healing among injured athletes. The last meta-analysis and systematic review still stands which had suggested that HBOT is ineffective for DOMS. The human studies are scarce despite widespread use of HBOT among athletes and require rigorous scientific studies before concluding if HBOT can facilitate the return to play of athletes.

We would like to thank you, Jason Kawalsky, for your revision in English.

Conflict of Interest: None. Dr. Hieda was supported by American Heart Association postdoctoral fellowship grant (18POST33960092) and the Harry S. Moss Heart Trust. The results of this review are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, we also admit that results of the present review do not constitute endorsement by ACSM.

REFERENCES

1. Weaver L. *Hyperbaric Oxygen Therapy Indications*. 13th ed. North Palm Beach (FL): Undersea and Hyperbaric Medical Society; 2014. p. 415.
2. Bennett M, Best TM, Babul S, Taunton J, Lepawsky M. Hyperbaric oxygen therapy for delayed onset muscle soreness and closed soft tissue injury. *Cochrane Database Syst Rev*. 2005;4:CD004713.
3. Staples J, Clement D. Hyperbaric oxygen chambers and the treatment of sports injuries. *Sports Med*. 1996;22(4):219–27.
4. Leach RM, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. *BMJ*. 1998;317(7166):1140–3.
5. Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med*. 2017;47(1): 24–32.
6. Yan L, Liang T, Cheng O. Hyperbaric oxygen therapy in China. *Med Gas Res*. 2015;5:3.
7. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg*. 2011;127(1 Suppl):131S–41.
8. Pittman RN. *Regulation of Tissue Oxygenation*. San Rafael, CA: Morgan & Claypool Life Sciences; 2011. p. 100.
9. Davis JC. Hyperbaric oxygen therapy. *J Intensive Care Med*. 1989; 4(2):55–7.
10. Sureda A, Batle JM, Martorell M, et al. Antioxidant response of chronic wounds to hyperbaric oxygen therapy. *PLoS One*. 2016;11(9):e0163371.
11. Ueno T, Omi T, Uchida E, Yokota H, Kawana S. Evaluation of hyperbaric oxygen therapy for chronic wounds. *J Nippon Med Sch*. 2014;81(1):4–11.
12. Guilliod RR, Pompeo MQ. Discussion: an update on the appropriate role for hyperbaric oxygen: indications and evidence. *Plast Reconstr Surg*. 2016;138(3 Suppl):117S–8.
13. Sunkari VG, Lind F, Botusan IR, et al. Hyperbaric oxygen therapy activates hypoxia-inducible factor 1 (HIF-1), which contributes to improved wound healing in diabetic mice. *Wound Repair Regen*. 2015;23(1):98–103.
14. Benincasa JC, de Freitas Filho LH, Carneiro GD, et al. Hyperbaric oxygen affects endothelial progenitor cells proliferation *in vitro*. *Cell Biol Int*. 2019;43(2):136–46.
15. Yang Y, Wei H, Zhou X, Zhang F, Wang C. Hyperbaric oxygen promotes neural stem cell proliferation by activating vascular endothelial growth factor/extracellular signal-regulated kinase signaling after traumatic brain injury. *Neuroreport*. 2017;28(18):1232–8.
16. Shaw FL, Winyard PG, Smerdon GR, Bryson PJ, Moody AJ, Eggleton P. Hyperbaric oxygen treatment induces platelet aggregation and protein release, without altering expression of activation molecules. *Clin Biochem*. 2009;42(6):467–76.

17. Heyboer M 3rd, Sharma D, Santiago W, McCulloch N. Hyperbaric oxygen therapy: side effects defined and quantified. *Adv Wound Care (New Rochelle)*. 2017;6(6):210–24.
18. Chawla A, Lavania AK. Oxygen toxicity. *Med J Armed Forces India*. 2001;57(2):131–3.
19. Donald KW. Oxygen poisoning in man. *Br Med J*. 1947;1(4506): 667; passim.
20. Sheridan RL, Shank ES. Hyperbaric oxygen treatment: a brief overview of a controversial topic. *J Trauma*. 1999;47(2):426–35.
21. Babul S, Rhodes EC. The role of hyperbaric oxygen therapy in sports medicine. *Sports Med*. 2000;30(6):395–403.
22. Kanhai A, Losito JM. Hyperbaric oxygen therapy for lower-extremity soft-tissue sports injuries. *J Am Podiatr Med Assoc*. 2003;93(4):298–306.
23. Petersen J, Holmich P. Evidence based prevention of hamstring injuries in sport. *Br J Sports Med*. 2005;39(6):319–23.
24. Kay MC, Register-Mihalik JK, Gray AD, Djoko A, Dompier TP, Kerr ZY. The epidemiology of severe injuries sustained by National Collegiate Athletic Association Student-Athletes, 2009–2010 through 2014–2015. *J Athl Train*. 2017;52(2):117–28.
25. Hamilton B, Alonso JM, Best TM. Time for a paradigm shift in the classification of muscle injuries. *J Sport Health Sci*. 2017; 6(3):255–61.
26. Burt DG, Twist C. The effects of exercise-induced muscle damage on cycling time-trial performance. *J Strength Cond Res*. 2011;25(8): 2185–92.
27. Cheung K, Hume P, Maxwell L. Delayed onset muscle soreness : treatment strategies and performance factors. *Sports Med*. 2003; 33(2):145–64.
28. Posner M, Cameron KL, Wolf JM, Belmont PJ Jr, Owens BD. Epidemiology of Major League Baseball injuries. *Am J Sports Med*. 2011; 39(8):1676–80.
29. Cameron KL, Owens BD. The burden and management of sports-related musculoskeletal injuries and conditions within the US military. *Clin Sports Med*. 2014;33(4):573–89.
30. Takeyama N, Sakai H, Ohtake H, Mashitori H, Tamai K, Saotome K. Effects of hyperbaric oxygen on gene expressions of procollagen, matrix metalloproteinase and tissue inhibitor of metalloproteinase in injured medial collateral ligament and anterior cruciate ligament. *Knee Surg Sports Traumatol Arthrosc*. 2007;15(4):443–52.
31. Borromeo CN, Ryan JL, Marchetto PA, Peterson R, Bove AA. Hyperbaric oxygen therapy for acute ankle sprains. *Am J Sports Med*. 1997;25(5):619–25.
32. Staples JR, Clement DB, Taunton JE, McKenzie DC. Effects of hyperbaric oxygen on a human model of injury. *Am J Sports Med*. 1999;27(5):600–5.
33. Mekjavic IB, Exner JA, Tesch PA, Eiken O. Hyperbaric oxygen therapy does not affect recovery from delayed onset muscle soreness. *Med Sci Sports Exerc*. 2000;32(3):558–63.
34. Harrison BC, Robinson D, Davison BJ, Foley B, Seda E, Byrnes WC. Treatment of exercise-induced muscle injury via hyperbaric oxygen therapy. *Med Sci Sports Exerc*. 2001;33(1):36–42.
35. Webster AL, Syrotuik DG, Bell GJ, Jones RL, Hanstock CC. Effects of hyperbaric oxygen on recovery from exercise-induced muscle damage in humans. *Clin J Sport Med*. 2002; 12(3):139–50.
36. Babul S, Rhodes EC, Taunton JE, Lepawsky M. Effects of intermittent exposure to hyperbaric oxygen for the treatment of an acute soft tissue injury. *Clin J Sport Med*. 2003;13(3):138–47.
37. Germain G, Delaney J, Moore G, Lee P, Lacroix V, Montgomery D. Effect of hyperbaric oxygen therapy on exercise-induced muscle soreness. *Undersea Hyperb Med*. 2003;30(2):135–45.
38. Brancaccio P, Lippi G, Maffulli N. Biochemical markers of muscular damage. *Clin Chem Lab Med*. 2010;48(6):757–67.
39. Bayer ML, Magnusson SP, Kjaer M. Tendon research group B. Early versus delayed rehabilitation after acute muscle injury. *N Engl J Med*. 2017;377(13):1300–1.
40. Oyaizu T, Enomoto M, Yamamoto N, et al. Hyperbaric oxygen reduces inflammation, oxygenates injured muscle, and regenerates skeletal muscle via macrophage and satellite cell activation. *Sci Rep*. 2018;8(1):1288.
41. Fujita N, Ono M, Tomioka T, Deie M. Effects of hyperbaric oxygen at 1.25 atmospheres absolute with normal air on macrophage number and infiltration during rat skeletal muscle regeneration. *PLoS One*. 2014;9(12):e115685.
42. Chaillou T, Lanner JT. Regulation of myogenesis and skeletal muscle regeneration: effects of oxygen levels on satellite cell activity. *FASEB J*. 2016;30(12):3929–41.
43. Horie M, Enomoto M, Shimoda M, Okawa A, Miyakawa S, Yagishita K. Enhancement of satellite cell differentiation and functional recovery in injured skeletal muscle by hyperbaric oxygen treatment. *J Appl Physiol (1985)*. 2014;116(2):149–55.
44. Bennett MH. Hyperbaric medicine and the placebo effect. *Diving Hyperb Med*. 2014;44(4):235–40.
45. Cervaens Costa Maia M, Camacho OF, Pinto Marques AF, Barata de Silva Coelho PM. Hyperbaric oxygen therapy treatment for the recovery of muscle injury induced in rats. *Diving Hyperb Med*. 2013;43(4):222–5.
46. Best TM, Loitz-Ramage B, Corr DT, Vanderby R. Hyperbaric oxygen in the treatment of acute muscle stretch injuries. Results in an animal model. *Am J Sports Med*. 1998;26(3):367–72.
47. Barata P, Cervaens M, Resende R, Camacho O, Marques F. Hyperbaric oxygen effects on sports injuries. *Ther Adv Musculoskelet Dis*. 2011;3(2):111–21.
48. Horn PC, Webster DA, Amin HM, Mascia MF, Werner FW, Fortino MD. The effect of hyperbaric oxygen on medial collateral ligament healing in a rat model. *Clin Orthop Relat Res*. 1999;360:238–42.
49. Ishii Y, Ushida T, Tateishi T, Shimojo H, Miyanaga Y. Effects of different exposures of hyperbaric oxygen on ligament healing in rats. *J Orthop Res*. 2002;20(2):353–6.
50. Yeh WL, Lin SS, Yuan LJ, Lee KF, Lee MY, Ueng SW. Effects of hyperbaric oxygen treatment on tendon graft and tendon-bone integration in bone tunnel: biochemical and histological analysis in rabbits. *J Orthop Res*. 2007;25(5):636–45.
51. Chan YS, Chen AC, Yuan LJ, et al. Effects of hyperbaric oxygen and platelet derived growth factor on medial collateral ligament fibroblasts. *Undersea Hyperb Med*. 2007;34(3):181–90.
52. Hsu RW, Hsu WH, Tai CL, Lee KF. Effect of hyperbaric oxygen therapy on patellar tendinopathy in a rabbit model. *J Trauma*. 2004;57(5):1060–4.
53. Mashitori H, Sakai H, Koibuchi N, et al. Effect of hyperbaric oxygen on the ligament healing process in rats. *Clin Orthop Relat Res*. 2004; 423:268–74.
54. Soolsma SJ. *The Effect of Intermittent Hyperbaric Oxygen on Short Term Recovery from Grade II Medial Collateral Ligament Injuries [dissertation]*. Vancouver, CA: University of British Columbia; 1996. p. 125.
55. Weaver LK, Churchill SK, Bell J, Deru K, Snow GL. A blinded trial to investigate whether 'pressure-familiar' individuals can determine chamber pressure. *Undersea Hyperb Med*. 2012;39(4):801–5.
56. Clarke D. Effective patient blinding during hyperbaric trials. *Undersea Hyperb Med*. 2009;36(1):13–7.
57. Lansdorp CA, van Hulst RA. Double-blind trials in hyperbaric medicine: a narrative review on past experiences and considerations in designing sham hyperbaric treatment. *Clin Trials*. 2018;15(5):462–76.