# Alternative Uses of Hyperbaric Oxygen Therapy in Military Medicine: Current Positions and Future Directions

*Adam T. Biggs, PhD*; Lanny F. Littlejohn, MD*; Hugh M. Dainer, PhD, MD†*

**ABSTRACT**

**Introduction:**

Hyperbaric oxygen therapy (HBOT) is a commonly used treatment for a variety of medical issues, including more than a dozen currently approved uses. However, there are alternative proposed uses that have significant implications among an active duty military or veteran population as treatments for PTSD, mild traumatic brain injury (mTBI), and traumatic brain injury (TBI). These applications have seen a recent groundswell of support from the operator and veteran communities, raising the visibility of using HBOT for alternative applications. The current review will cover the existing evidence regarding alternative uses of HBOT in military medicine and provide several possibilities to explain the potential conflicting evidence from empirical results.

**Materials and Methods:**

There were no inclusion or exclusion criteria for articles addressing currently approved HBOT uses as covered under the military health system. These references were provided for comparison and illustration as needed. For alternative HBOT uses, the review focuses explicitly upon three alternative uses in PTSD, mTBI, and TBI. The review addresses any piece of case study evidence, observational data, quasi-experimental design, or randomized-controlled trial that explored any or a combination of these issues within an active duty population, a veteran population, or a civilian population.

**Results:**

The existing medical evidence does not support a consensus viewpoint for these alternative uses of HBOT. Based on the literature review, there are four competing positions to explain the lack of consistency among the empirical results. These possibilities are described in no particular order. First, an explanation suggests that the results are because of placebo effects. The combination of participant expectations and subjective symptom reporting creates the potential that reported improvements are because of placebo rather than casual mechanisms. Second, another position suggests that experiments have utilized sham conditions which induced therapeutic benefits. If sham conditions have actually been weakened active treatment conditions, rather than placebo controls, it could explain the lack of observed significant differences in randomized clinical trials. Third, there has been a substantial amount of heterogeneity both in the symptoms treated and the treatments applied. This heterogeneity could explain the inconsistency of the data and the difficulty in reaching a consensus viewpoint. Fourth, the HBOT treatments may actively treat some tangential medical issue the patient is having. The treatment would thus promote an environment of healing without directly treating either PTSD, mTBI, or TBI, and the reduction in orthogonal medical issues facilitates a pathway to recovery by reducing tangential medical problems.

**Conclusions:**

The mixed empirical evidence does not support recommending HBOT as a primary treatment for PTSD, mTBI, or TBI. If applied under the supervision of a licensed military medical professional, the consistently safe track record of HBOT should allow it to be considered as an alternative treatment for PTSD, mTBI, or TBI once primary treatment methods have failed to produce a benefit. However, the evidence does warrant further clinical investigation with particular emphasis on randomized clinical trials, better placebo controls, and a need to develop a consistent treatment protocol.

## INTRODUCTION

Hyperbaric oxygen therapy (HBOT) describes a technique wherein patients breathe air with above average oxygen concentration in a pressurized environment, usually a tube or chamber. The intent is to increase blood oxygen levels as a means to facilitate healing. This technique is already well established, and there are currently 13 FDA cleared uses for hyperbaric chambers, including treatment of air or gas

*Naval Special Warfare Command, Medical Department, Coronado, CA 92155, USA

†Naval Special Warfare Group FOUR Medical Department, Virginia Beach, VA 23521, USA

The views expressed in this article reflect the results of research conducted by the author and do not necessarily reflect the official policy or position of the Department of the Navy, the DoD, or the U.S. Government.



doi:10.1093/milmed/usab022

embolism, carbon monoxide poisoning, decompression sickness, and radiation necrosis.[1] Although there are HBOT uses supported by the FDA, there are also claims by various organizations and individuals which extend beyond these established uses. Examples of more controversial treatments include the potential for HBOT treatments of cancer, mild traumatic brain injury (mTBI), and Alzheimer's disease. The goal of this review is to consider the available evidence regarding HBOT to include case studies and randomized, placebo-controlled studies when evaluating the possible alternative uses of HBOT in military patients.

## HOW DOES HBOT AFFECT THE PATIENT?

The direct biological impact of HBOT is to increase the amount of oxygen carried within the blood and into body tissues. Under normal pressure at the sea level, defined as 1 atmosphere (1 ATA), the proportion of oxygen in the blood is most heavily dependent on saturated or oxygen-laded hemoglobin as a result of the partial pressure to which the blood is exposed. Partial pressure of the oxygen is typically high in the lungs and readily causes oxygen to bind to any available hemoglobin, but in other tissues, lower partial pressures causes the oxygen to be released from hemoglobin directly into the bloodstream and allows oxygenation of body tissues. This relationship produces a sigmoid plot, where there is a non-linear relationship between hemoglobin saturation and the partial pressure of oxygen. Many other factors besides the partial pressure of oxygen can affect this relationship, including carbon monoxide[2] and temperature,[3] although pressure and oxygen concentration are considered the critical factors.

Hyperbaric oxygen therapy combines these factors by both increasing oxygen concentration of the air and increasing relative pressure, which in turn maximizes the ability of hemoglobin to saturate with oxygen. Moreover, the increased pressure of HBOT is important because simply breathing gas with higher than normal oxygen levels, normobaric oxygen therapy, is less effective in increasing the oxygen capacity of the blood.[4] This effect is because of higher levels of oxygen that dissolve directly in blood serum at pressures greater than 1 ATA. See Fig. 1. The end product is that HBOT causes higher levels of oxygen to reach tissues throughout the body, not only through oxyhemoglobin, but also because of oxygen dissolved directly in the serum.

In clinical practice, patients enter a hyperbaric tube or environment that could be designed for a single user (monoplace chamber) or for multiple individuals (multiplace chamber) to use simultaneously. Patients then breathe gas with increased oxygen concentration anywhere up to 100% compared to the 21% oxygen concentration of normal air while experiencing an environment with increased pressure. For HBOT, common pressures include up to 3.0 ATA, although the precise value used during treatment varies significantly by treatment regimen, device, and conditions being treated.[5] Increased pressure allows, among other things, more oxygen to be carried in

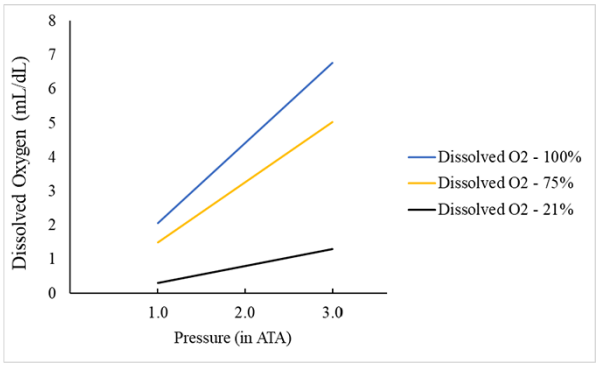


**FIGURE 1.** Dissolved oxygen concentration in blood across different inspired oxygen levels and pressures. Top line indicates result under 100% inspired oxygen level, middle line indicates result under 75% inspired oxygen level, and bottom line indicates result under 21% inspired oxygen level.

solution. This state produces greater oxygenation because oxygen in solution can reach obstructed areas through which red blood cells could not pass as well as enabling oxygenation under conditions with impaired oxygen transportation via hemoglobin, such as carbon monoxide poisoning.[6]

To describe with greater precision, patients breathing normobaric air typically have arterial oxygen tensions of ~100 mmHg and tissue oxygen tension of ~55 mmHg, whereas the combination of 100% oxygen at 2.0-3.0 ATA can produce arterial oxygen tension in excess of 2,000 mmHg and oxygen tension within tissues of almost 400 mmHg.[7] These levels have numerous cellular and physiological benefits to a recovering patient. Wound healing becomes expedited through angiogenesis, facilitating the migration of macrophages and speeding epithelialization.[8] These factors ultimately maintain tissue viability while reducing the possibility of infection and potentiating more beneficial recovery conditions. However, despite these multiple mechanisms of action which might enhance patient recovery, therapeutic benefits are rarely attained from a single visit with some conditions requiring between 20 and 40 treatments.[9]

Modern HBOT is usually a safe procedure, with protocols written to avoid the physical danger of combustion in an oxygen-rich environment and physiological danger of toxic exposures. Even so, there are some potential side effects the patient may experience. Common effects include middle ear barotrauma because of the pressure changes, which can cause ear pain, general discomfort, and difficulty with ear equalization.[10] These middle ear effects are typically mild and can be mitigated or avoided with proper ear clearing and appropriate compression rates. The closeness of the space could conceivably induce claustrophobia, which is dependent more on the combination of the specific chamber and individual than anything generalizable to HBOT at large. Some more extreme side effects can occur, such as central nervous system oxygen toxicity (seizure), pulmonary oxygen toxicity (tracheobronchitis, edema, and fibrosis), and ocular toxicity (decreased,

though typically temporary, visual acuity), but these issues are rare with modern treatment protocols.[10]

## EVIDENCE CONCERNING HYPERBARIC OXYGEN THERAPY: APPROVED USES

Even though HBOT has previously been demonstrated as a safe and reliable method to increase oxygenation and facilitate healing, the controversial issues arise when discussing the evidence for and against some of its potential uses. The best evidence supporting HBOT comes in established medical uses that have already received various approval or cleared uses by governing bodies such as the FDA or professional medical organizations. There are currently 13 FDA-cleared uses for HBOT chambers: air or gas embolism, carbon monoxide poisoning, clostridal myositis, crush injury or other acute traumatic ischemias, decompression sickness (bends), enhancement of healing in select wounds, exceptional blood loss (severe anemia), intracranial abscess, necrotizing soft tissue infections, osteomyelitis, delayed radiation injury, skin grafts and flaps, and thermal burns.[11] Within these FDA-cleared options, there remain numerous questions about the most efficacious usage of HBOT. For example, there are questions as to the duration of benefits and which treatment time window is best administered for optimal impact. Some evidence attained from patients with diabetic foot ulcers suggested more benefits of HBOT in short-term usage compared to long-term issues,[12] which aligns with research that HBOT has neuroprotective effects when administered within the acute phase of trauma.[13]

Despite the FDA-cleared uses and evidence supporting them, individual treatment regimens differ in pressure applied, time of treatment, number of treatments, and overall benefit to be anticipated from HBOT. The latter point is particularly important as it will impact choices among treatment options and associated costs. The empirical literature suggests that some benefit should be conferred, yet the scope and scale of such facilitated healing continue to be a subject of debate. One study observed a reduction in ulcer area between 33% and 62% when treating diabetic foot ulcer across a variety of protocols,[12] although, even in these uses, the authors concluded that further research was necessary to address experimental shortcomings. It is possible to selectively choose from various studies and observe comparable benefits in diseases ranging from cardiac ischemia to neonatal hypoxia,[14] yet moderate improvement is a reasonable expectation within the same repeated caveat. Specifically, improvements are regularly observed following HBOT in the various FDA-cleared uses for the treatment with the understanding that anticipated benefits vary substantially. Ultimately, an important interpretation is that many of the current HBOT uses counter some state in which the patient suffers from oxygen deficiencies or would otherwise benefit from the body's response to increased oxygenation.

## EVIDENCE CONCERNING HYPERBARIC OXYGEN THERAPY: PTSD, MTBI, AND TBI

Discussion and research continue regarding uses not currently on the FDA-cleared list. The most significant discussion appears to be regarding the evidence for and against using HBOT as a treatment for PTSD, traumatic brain injury (TBI), or mild traumatic brain injury (TBI). There are additional ongoing clinical investigations regarding autism and cerebral palsy with a robust literature that likewise includes widely variable results. However, the remainder of this discussion will focus on PTSD and mTBI/TBI as the more relevant treatment needs for military medicine, and literature concerning other disorders such as autism and cerebral palsy will not be reviewed here (The website https://clinicaltrials.gov/ offers a searchable database of ongoing publicly funded and privately funded clinical trials. To explore current clinical trials involving HBOT beyond mTBI, TBI, and PTSD, we recommend searching this website.).

The evidence for HBOT in PTSD/mTBI/TBI is controversial because the results are so mixed in the empirical literature and strong proponents exist both for and against the method. Preliminary evidence supporting the use of HBOT for these conditions comes from case studies with anywhere between 1 and 6 patients as a part of the treatment. These examples demonstrate improvements in neuropsychological functioning for mTBI,[15] chronic TBI,[16,17] and improvements in PTSD symptoms.[18,19] Alternatively, some case studies could caution medical professionals about rare complications such as tension pneumocephalus because of unrepaired skull fractures.[20]

However, this evidence should be interpreted with caution for several reasons. The primary reason is that causal factors are much more difficult to isolate in case studies compared to randomized, placebo-controlled studies, which limits the conclusions that can be made from these observations. Additionally, case studies are inherently prone to publication bias.[21] The point being that suggestive or exciting results tend to be published, whereas the failures and less surprising outcomes tend to be withheld. Substantial improvements and rare complications both fall into the more evocative category and increase the visibility of these cases through a publication bias. Even so, case study evidence should be considered alongside the greater contextual evidence supporting or refuting HBOT for these more controversial conditions, but this evidence should be considered alongside the results of more carefully controlled clinical investigations in humans.

Several clinical trials primarily dealing with post-concussion syndrome have demonstrated significant improvements in cognitive testing and quality of life assessments following HBOT treatments.[22,23] Patients undergoing HBOT or even a combined hyperbaric hyperoxia and normobaric hyperoxia treatment[24] have exhibited reduced mortality rates and numerous beneficial conditions to include increased cerebral blood flow.[25] There are also some pieces of empirical

evidence to support underlying mechanisms that might provide causal factors to explain these improvements. Notably, HBOT can induce neuroplasticity through angiogenesis and nerve fiber regeneration in patients who have suffered TBI while potentially reducing inflammatory responses.[26] Retrospective studies have likewise reviewed patient records and concluded that there are significant benefits to the use of HBOT for TBI patients and others suffering from post-concussive symptoms.[27] These studies also identify several unknowns about the treatment, such as the duration of these benefits. One study demonstrated significant improvements in post-concussive and PTSD symptoms, yet these benefits lasted less than 6 months.[28] This issue will in turn inherently affect the required duration of any treatment regimen and the expected impact on long-term quality of life.

The primary counterevidence to these claims comes from randomized clinical trials that attempt to use sham conditions to address the possibility of placebo effects. Essentially, case studies and some empirical studies typically provide an active condition for HBOT with increased inspired oxygen concentration under increased atmospheric pressure. Randomized clinical trials also tend to provide a corresponding sham or placebo condition that administers a variant of the active condition to make any improvements because of patient anticipation. These control conditions vary, but each approach tends to provide one of the following: a sham control with pressured, but non-hyperbaric environment; inspired oxygen rates lower than room air; both partial pressure and lower oxygen rates; or some combination thereof to create a condition intended to simulate normal breathing or at least watered-down hyperbaric conditions. Hyperbaric oxygen therapy treatments have failed to produce greater benefits than sham treatments across several randomized clinical trials for those trials that included more rigorous control conditions.[29–33] Although both HBOT and sham treatments typically produced improved performance on cognitive or symptomatic evaluations, the clinical trials ultimately concluded that the benefits of HBOT were not significantly better than a sham treatment. Some researchers and clinicians may therefore conclude that HBOT is equivalent to sham treatment.

## WHY SO MUCH CONTRADICTING EVIDENCE FOR HBOT IN PTSD, MTBI, AND TBI?

The evidence thus far provides very disparate findings when HBOT is specifically evaluated in the context of PTSD or as a therapy following a post-concussive event—either of which have significant implications for military medicine. Unfortunately, there are multiple discrepancies between studies that prevent simple comparisons between conditions. For example, some studies utilize a normal treatment course without pressurized chamber intervention as well a sham condition, whereas other studies utilize equivalent pressure conditions with different inspired oxygen levels. The majority of studies follow a treatment regimen of 40 sessions across 6-8 weeks, although there are exceptions to this too as some studies will utilize fewer sessions. Differences across treatment types and sham conditions substantially complicate any consensus across these incongruent results. However, there are currently four primary positions which could be offered as possibilities to explain the current findings: (1) placebo effects, (2) active sham treatments, (3) treatment heterogeneity, and (4) the facilitation argument. Each position will be discussed in turn for its relevance to the wider conversation.

### *Placebo Effects*

One position argues against the effectiveness of HBOT treatments by suggesting the observed improvements are largely, if not solely, because of placebo effects. This evidence is supported by the failure of HBOT to produce greater than sham benefits across multiple randomized, clinical trials when the procedure is compared to a sham intervention.[29–33] A sham condition is essential in these randomized clinical trials for several reasons. Foremost, simple observation over time could be masked by natural healing during the same period, and a control condition provides an important comparison against the intervention technique. Second, any intervention is regularly anticipated to produce improvement because of the expectations of the individual patient. This improvement could be in the form of a placebo effect, where a patient's belief in the treatment facilitates improvement under the treatment regimen, or a Hawthorne effect, where the patient is reacting differently because of the presence of an observer during the evaluation.[34] Each factor could be impacting the results in a different way. For example, patients can readily feel the pressure change and therefore predict when they are undergoing the treatment condition, which is why a pressure of at least 1.2 ATA is recommended to mask the pressurization process.[35] The Hawthorne effect is particularly important for clinical evaluations assessing symptomology because an individual patient may report fewer symptoms simply because of their awareness of the evaluation or an attempt, conscious, or unconscious, to align with what they believe to be the desired result.

These combined possibilities could produce seeming improvements in cognitive or symptomatic reports following HBOT despite no reliable causal change in the individual that would support prolonged benefits of treatment. Sham or control comparisons are the best way to prevent, reduce, or categorize the scope of placebo effects, and when an active HBOT condition fails to outperform the sham pressure condition in a double-blind, placebo-controlled study, a logical conclusion is that any observed benefits are because of some form of placebo effect and not because of a true clinical improvement in the patient's condition.

### *Active Sham Treatments*

The counterargument to the placebo effects position is that many of the sham conditions used in randomized clinical trials are not actually sham conditions—they are inadvertently

active conditions that likewise produce a therapeutic benefit.[36] This argument is sometimes referred to colloquially as the "sham-is-not-a-sham" position. Under this premise, active conditions are not outperforming sham conditions because the "sham" conditions are actually producing a reliable, albeit smaller, treatment effect contributing to greater difficulty in achieving a statistically significant difference between conditions. This argument could be a factor in combined conditions of higher pressure and inspired oxygen levels greater than room air. Pressurizing air between 1.2 and 1.3 ATA produces between a 33% and 49% increase in dissolved oxygen in the bloodstream. Combined with the lack of guidelines for oxygen and pressure combinations among this alternative treatment, supposedly sham conditions could increase dissolved oxygen content in the bloodstream (e.g., because of increased pressure intended to simulate full treatment pressurization) and induce similar therapeutic conditions to the actual active treatment. If studies are not suitably powered to detect statistical differences between two active treatment conditions of varying effect size, then the result would be a non-statistically significant difference for a real effect.

### *Treatment Heterogeneity*

Some authors suggest that the heterogeneity of human TBI and issues with multiple factors, such as delayed treatment timeline and subjective methods in outcome measurement, could produce a misinterpretation of the results.[37] This argument could explain both the mixed findings of the previous literature and why an otherwise effective treatment regimen might not generate reliable improvements during patient recovery. TBI and mTBI research inherently have variability in observed symptoms because concussive events rarely produce the exact same symptomology or the same severity. The variance is ultimately addressed through multiple studies and replication (or failure to replicate), which should overcome the issue of variance in symptomology. HBOT research does not have sufficient volume of empirical evidence to make conclusive statements across symptom severity. Similarly, there are issues in the heterogeneity of the treatments themselves, with varying pressurized levels between 1.5 and 3.0 ATA in the HBOT condition as well as differences in both the number of sessions and length of individual sessions. The empirical literature is still addressing potential efficacy of HBOT in general, and treatment heterogeneity contributes to further confusion among the results. In short, the treatment heterogeneity argument suggests that there is not sufficient evidence to come to a definitive conclusion regarding HBOT efficacy because the HBOT treatments have not been applied consistently.

### *Facilitation Argument*

There is empirical and mechanistic evidence available that HBOT can produce neurologically significant benefits to a patient.[15–17] These benefits are well-evidenced through FDA-cleared uses of the treatment regimen[7] and through studies demonstrating neuroplasticity or other neurological benefits at a cellular level.[13,26] As such, there is one possibility that HBOT intervention will produce some therapeutic effect by improving the health of an individual following a traumatic event that caused either general physiological impairments or psychological distress. If the individual experiences cognitive and general mental functioning improvements or physiological improvements following HBOT treatment, these improvements could facilitate recovery by removing obstacles in their daily lives. By this position, there are no direct mechanistic relationships to PTSD or psychological impairments, but the treatment may address tangential cognitive or psychological issues from which the patient is suffering. In turn, the absence of additional neurological challenges facilitates and smooths a pathway to recovery. This position would explain why there is some mechanistic evidence for neurological improvement while still producing mixed results in clinical trials when orthogonal or comorbid issues are not fully addressed. However, we should note that this position is only speculative. The facilitation argument ostensibly calls for more latent variable analyses to address indirect effects in HBOT studies and discount alternative explanations.

## SUMMARY AND CONCLUSIONS

Hyperbaric oxygen therapy is recognized as a safe, commonly used medical procedure. However, there is an ongoing debate among the medical literature regarding the efficacy of HBOT as a potential treatment for PTSD, mTBI, and TBI. Reviews and opinions cover both sides of the argument with individuals claiming both sufficient support to pursue HBOT as a treatment for these issues[36] and highly critical opinions challenging HBOT intervention as a waste of time, waste of money, and providing false hope to impaired servicemembers.[38] At present, multiple DoD reviews from the Government Accountability Office[39] and the Department of Veteran's Affairs[11] have considered the evidence and concluded that the robust treatment benefits observed in individual case studies have not been evident in controlled, randomized clinical trials, thereby failing to reach a sufficient level of scientific evidence mandating or supporting this treatment for medically prescribed applications as far as PTSD, mTBI, and TBI are concerned.

The strongest evidence supporting HBOT has been produced by case studies and animal models that help support mechanisms by which HBOT could impact neurological functioning. Unfortunately, these findings have failed to transition well into human clinical trials, instead producing highly mixed results regarding the efficacy of the treatment. The current, most reliable conclusion is that HBOT can be safely used for its FDA-cleared applications, and while its minimal risks make it a potential adjunct treatment regimen for other issues to include PTSD, mTBI, and TBI, there is not sufficient clinical evidence at the present time to support its use as a

primary treatment method for post-concussive issues following military deployment or blast exposure. That said, given the thorough track record of safety for HBOT when overseen by a licensed military professional, consideration for HBOT as an alternative treatment is reasonable on a case-by-case basis—particularly where standard treatments have failed to produce significant improvements, understanding that these treatments may not be covered financially by the military health system.

## SEARCH PROCESS AND INCLUSION CRITERIA

Preliminary searches began with published reviews of the HBOT literature with specific emphasis on three alternative uses: mTBI, TBI, and PTSD. "Hyperbaric oxygen therapy" was entered into multiple databases such as PubMed and Google Scholar, along with the additional terms of "mild traumatic brain injury," "traumatic brain injury," or "post-traumatic stress disorder." This review had no limitations based upon case study evidence, observational data, quasi-experimental design, or randomized-controlled trial that explored any or a combination of these issues within an active duty population, a veteran population, or a civilian population. There were no inclusion or exclusion criteria for articles addressing currently approved HBOT uses as covered under the military health system. Each reference was included to support of an illustrative point of existing uses or to describe the process of administering hyperbaric oxygen. References were constrained only by the maximum permissible amount under this journal format.

## FUNDING

No external funding was received for this work.

## CONFLICT OF INTEREST STATEMENT

The authors declare no financial or non-financial conflicts of interest.

## SOURCE OF SUPPORT

None declared.

## HUMAN RESEARCH

No human subjects research was involved in this review.

## REFERENCES

1. Food and Drug Administration Consumer Update: Hyperbaric oxygen therapy: don't be misled. 2013. Available at https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-dont-be-misled, August 23; accessed September 12, 2019.
2. Barker SJ, Tremper KK: The effect of carbon monoxide inhalation on pulse oximetry and transcutaneous PO2. Anesthesiology 1987; 66(5): 677-9.
3. Knowles TP, Mullin RA, Hunter JA, Douce HF: Effects of syringe material, sample storage time, and temperature on blood gases and oxygen saturation in arterialized human blood samples. Respir Care 2006; 51(7): 732-6.
4. Eve DJ, Steele MR, Sanberg PR, Borlongan CV: Hyperbaric oxygen therapy as a potential treatment for post-traumatic stress disorder associated with traumatic brain injury. Neuropsychiatr Dis Treat 2016; 12:(2016) 2689.
5. Mathieu D, Neviere R, Pellerin P, Patenotre P, Wattel F: Pedicle musculocutaneous flap transplantation: prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. Plast Reconstr Surg 1993; 91(2): 329-34. PMID: 8430149.
6. Gill AL, Bell CN: Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM 2004; 97(7): 385-95.
7. Tibbles PM, Edelsberg JS: Hyperbaric-oxygen therapy. N Engl J Med 1996; 334(25): 1642-8.
8. Kindwall EP, Gottlieb LJ, Larson DL: Hyperbaric oxygen therapy in plastic surgery: a review article. Plast Reconstr Surg 1991; 88(5): 898-908.
9. Mayo Clinic: Hyberbaric oxygen therapy. Available at https://www.mayoclinic.org/tests-procedures/hyperbaric-oxygen-therapy/about/pac-20394380, January 12, 2018; accessed September 13, 2019.
10. Plafki C, Peters P, Almeling M, Welslau W, Busch R: Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med 2000; 71(2): 119-24.
11. Peterson K, Bourne D, Anderson J, Boundy E, Helfand M: Evidence brief: Hyperbaric Oxygen Therapy (HBOT) for traumatic brain injury and/or post-traumatic stress disorder. In: *VA Evidence Synthesis Program Evidence Briefs [Internet]*. Department of Veterans Affairs; 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499535/; accessed February 02, 2021.
12. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S: Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2015; 6.
13. Lin KC, Niu KC, Tsai KJ, et al: Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. J Trauma Acute Care Surg 2012; 72(3): 650-9.
14. Shahriari A, Khooshideh M, Heidari M: Diseases treated with hyperbaric oxygen therapy; a literature review. Med Hypothesis Discovery Innovation Interdiscip Sci J 2014; 1(2).
15. Wright CJK, Zant E, Groom K, Schlegel RE, Gilliland K: Case report treatment of mild traumatic brain injury with hyperbaric oxygen. Undersea Hyperbaric Med 2009; 36(6): 391-99.
16. Hardy P, Johnston KM, De Beaumont L, et al: Pilot case study of the therapeutic potential of hyperbaric oxygen therapy on chronic brain injury. J Neurol Sci 2007; 253(1-2): 94-105.
17. Stoller KP: Hyperbaric oxygen therapy (1.5 ATA) in treating sports related TBI/CTE: two case reports. Med Gas Res 2011; 1(1): 17.
18. Improvement of PCS and PTSD following SPECT and HBOT. Harch PG, Fogarty PG, Staab PK, Van Meter K: Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post traumatic stress disorder: a case report. Cases J 2009; 2(1): 6538.
19. Improvement in PTSD symptoms, Eovaldi B, Zanetti C: Hyperbaric oxygen ameliorates worsening signs and symptoms of post-traumatic stress disorder. Neuropsychiatr Dis Treat 2010; 6(1): 785.
20. Lee LC, Lieu FK, Chen YH, Hung TH, Chen SF: Tension pneumocephalus as a complication of hyperbaric oxygen therapy in a patient with chronic traumatic brain injury. Am J Phys Med Rehabil 2012; 91(6): 528-32.
21. Easterbrook PJ, Gopalan R, Berlin JA, Matthews DR: Publication bias in clinical research. Lancet 1991; 337(8746): 867-72.
22. Boussi-Gross R, Golan H, Fishlev G, et al: Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury-randomized prospective trial. PLoS One 2013; 8(11): e79995.
23. Harch PG, Andrews SR, Fogarty EF, et al: A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma 2012; 29(1): 168-85.

24. Rockswold SB, Rockswold GL, Zaun DA, Liu J: A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. J Neurosurg 2013; 118(6): 1317-28.
25. Rockswold SB, Rockswold GL, Zaun DA, et al: A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. J Neurosurg 2010; 112(5): 1080-94.
26. Tal S, Hadanny A, Sasson E, Suzin G, Efrati S: Hyperbaric oxygen therapy can induce angiogenesis and regeneration of nerve fibers in traumatic brain injury patients. Front Hum Neurosci 2017; 19(11): 508.
27. Hadanny A, Abbott S, Suzin G, Bechor Y, Efrati S: Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis. BMJ Open 2018; 8(9): e023387.
28. Weaver LK, Wilson SH, Lindblad AS, et al: Hyperbaric oxygen for post-concussive symptoms in United States military service members: a randomized clinical trial. Undersea Hyperbaric Med 2018; 45(2): 129-56.
29. Wolf G, Cifu D, Baugh L, Carne W, Profenna L: The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma 2012; 29(17): 2606-12.
30. Cifu DX, Hart BB, West SL, Walker W, Carne W: The effect of hyperbaric oxygen on persistent postconcussion symptoms. J Head Trauma Rehabil 2014; 29(1): 11-20.
31. Wares JR, Cifu DX, Hoke KW, Wetzel PA, Gitchel G, Carne W: Effects of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. J Rehabil Res Dev 2014; 51(7): 1047-56.
32. Cifu DX, Walker WC, West SL, et al: Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes. Ann Neurol 2014; 75(2): 277-86.
33. Miller RS, Weaver LK, Bahraini N, et al: Effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. JAMA Intern Med 2015; 175(1): 43-52.
34. Adair JG: The Hawthorne effect: a reconsideration of the methodological artifact. J Appl Psychol 1984; 69(2): 334-45.
35. Weaver LK, Bell J, Deru K: A blinded trial to investigate whether 'pressure-familiar' individuals can determine chamber pressure. Undersea Hyperbaric Med 2012; 39(4): 801-5.
36. Figueroa XA, Wright JK: Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. Neurology 2016; 87(13): 1400-6.
37. Hu Q, Manaenko A, Xu T, Guo Z, Tang J, Zhang JH: Hyperbaric oxygen therapy for traumatic brain injury: bench-to-bedside. Med Gas Res 2016; 6(2): 102-10.
38. Bennett MH: Evidence brief: Hyperbaric Oxygen Therapy (HBOT) for traumatic brain injury and/or post-traumatic stress disorder. Diving Hyperb Med 2018; 48(2): 115.
39. Government Accountability Office: Research on hyperbaric oxygen therapy to treat traumatic brain injury and post-traumatic stress disorder. Available at https://www.gao.gov/assets/680/674334.pdf, December 2015; accessed September 16, 2019.