

Hyperbaric oxygen

B-level evidence in mild traumatic brain injury clinical trials

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ABSTRACT

Objective: First, to demonstrate that B-level evidence exists for the use of hyperbaric oxygen therapy (HBOT) as an effective treatment in mild to moderate traumatic brain injury/persistent post-concussion syndrome (mTBI/PPCS). Second, to alert readers and researchers that currently used pressurized air controls ($\geq 21\%$ O₂, >1.0 ATA) are therapeutically active and cannot be utilized as sham controls without further validation.

Method: Review of published, peer-reviewed articles of HBOT prospective and controlled clinical trials of mTBI/PPCS symptoms.

Results: Published results demonstrate that HBOT is effective in the treatment of mTBI/PPCS symptoms. Doses of oxygen that are applied at $\geq 21\%$ O₂ and at pressures of >1.0 ATA produce improvements from baseline measures. Some of the recently published clinical trials are mischaracterized as sham-controlled clinical trials (i.e., sham = 21% O₂/1.2–1.3 ATA), but are best characterized as dose-varying (variation in oxygen concentration, pressure applied, or both) clinical trials.

Conclusions: Hyperbaric oxygen and hyperbaric air have demonstrated therapeutic effects on mTBI/PPCS symptoms and can alleviate posttraumatic stress disorder symptoms secondary to a brain injury in 5 out of 5 peer-reviewed clinical trials. The current use of pressurized air (1.2–1.3 ATA) as a placebo or sham in clinical trials biases the results due to biological activity that favors healing. *Neurology*® 2016;87:1-7

GLOSSARY

DoD = Department of Defense; **HBA** = hyperbaric air; **HBO** = hyperbaric oxygen; **HBOT** = hyperbaric oxygen therapy; **mTBI** = mild traumatic brain injury; **PPCS** = persistent postconcussion syndrome; **PTSD** = posttraumatic stress disorder; **TBI** = traumatic brain injury; **VA** = Veterans Administration.

The use of hyperbaric oxygen (HBO) as a therapy for brain injuries has been tested infrequently and in a fashion not congruent with evidence-based medicine for many years. This has changed since 2008, with clinical trials testing HBO under sponsorship of the Department of Defense (DoD)/Veterans Administration (VA) and Army or under civilian initiative. The common purpose of these clinical trials was to assess the clinical efficacy of HBO therapy (HBOT) on postacute mild traumatic brain injury (mTBI)/persistent postconcussion syndrome (PPCS). Several earlier articles (pre-2010) have presented patient outcome studies^{1–9} and retrospective analyses^{10–12} that report positive effects of HBO on traumatic brain injury (TBI) and neurologic head injuries. Since 2012, a new series of clinical trials^{13–19} have demonstrated that HBO has reparative effects for mTBI/PPCS symptoms and cognitive deficits.

Study results to date have been clouded by confusion regarding what constitutes an effective sham. Broadly divided, the DoD/VA/Army-sponsored trials utilized pressurized air groups as sham controls, while civilian-led studies utilized crossover designs or baseline comparators to assess improvement. Assumptions made on the use of certain controls by the DoD/VA/Army-sponsored studies has led some of the study authors to conclude no effect was present, when there was actually a significant improvement in primary and secondary endpoints.

From the Brain Health & Healing Foundation (X.A.F.), Seattle; and Swedish Medical Center (J.K.W.), Wound Healing & Hyperbarics, Edmonds, WA. Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

RESULTS OF THE HBOT CLINICAL TRIALS Four pivotal US-based clinical trials and one Israeli-based clinical trial have provided well-structured and controlled studies that demonstrate reparative effects in mTBI/PPCS symptoms with HBOT. Improvements in TBI and posttraumatic stress disorder (PTSD) symptom scores for the 2 DoD/VA-sponsored studies,^{15,16,20} the Army-sponsored study of Miller et al.,¹⁴ a civilian-sponsored study of Harch et al.,¹⁸ and the Israeli civilian study of Boussi-Gross et al.¹⁹ have demonstrated both clinical and statistically significant improvements from baseline measures after undergoing 30–40 1-hour HBOT treatments during the course of the trials. All participants had documented TBIs and were at least 2 years into the PPCS phase of the injury, ensuring that spontaneous recovery was a highly unlikely factor.

The DoD/VA/Army^{14–16,20} and civilian¹⁸ studies provide valuable cross-study comparable measures in 4 reported clinical trials. The Rivermead Post-Concussion Questionnaire, Immediate Post-Concussion Assessment and Cognitive Testing, and PTSD Checklist–Military were used as primary and secondary endpoint measures in all the US studies. Although the DoD/VA/Army-sponsored study authors characterize their studies as sham-controlled, the studies are best classified as dose- and pressure-varying trials. When analyzed as individual groups, the results (figure 1, left) are scattershot and uninformative. However, a dose curve emerges when the study results are arranged by the amount of relative dissolved oxygen that participants experienced (figure 1, right), a clear indication that HBOT is having a drug-like effect in brain injury repair. The graphs on the right (figure 1) are grouped into relative levels of dissolved oxygen in plasma. The numbers under each group (1, 1.15, 8.6, 11.5, and 13.75) represent the multiplier of the average amount of dissolved oxygen above 1.0 ATA, 21% O₂ that is in the plasma (e.g., –8.6 is 8.6 times greater than the amount of plasma dissolved at 1.0 ATA, 21% O₂).

The clinical improvements seen in the participants are large and consistent through each of the studies. The apparent dose response profile strongly suggests that lower pressures (≤ 2.0 ATA) and lower oxygen levels ($< 100\%$ O₂) are potentially better for mTBI/PPCS and PTSD symptom recovery. Like prescription drugs, there is a Goldilocks zone when using HBOT (or hyperbaric air [HBA]) for treating mTBI/PPCS: too much may impair repair mechanisms; too little may not provide sufficient support; just right ensures that repair mechanisms are optimized.

The use of unproven shams has led to conclusions of inactivity in the current literature. For example, the published articles by Wolf et al.,²⁰ Cifu et al.,^{15,16} and Miller et al.¹⁴ contended that the observed improvements of HBOT (and HBA) were a placebo effect

due to the ritual of HBO.²¹ Yet the controls that were applied to these studies have known biological activity.²² A recurrent objection by study authors that incorrectly assumed the control groups they selected were inactive is best exemplified in the following:

We recognize that a sham is not inert, and we cannot completely discount the physiological effects of minimal increases in nitrogen or oxygen from pressurized room air. However, we believe it is biologically implausible that air at 1.2 ATA (equivalent to 2 m of seawater pressure) has a beneficial effect on healing the damaged brain remotely after mTBI.¹⁴

Positive improvements from pretreatment (baseline) measures are observed in all the DoD/VA/Army and civilian studies. The measured responses to both HBO and HBA treatment groups are therapeutic, but a minimal effective dose of O₂ + pressure has not been established in the hyperbaric medical literature. Thus, the use of a sham is problematic and confounding for study interpretation.

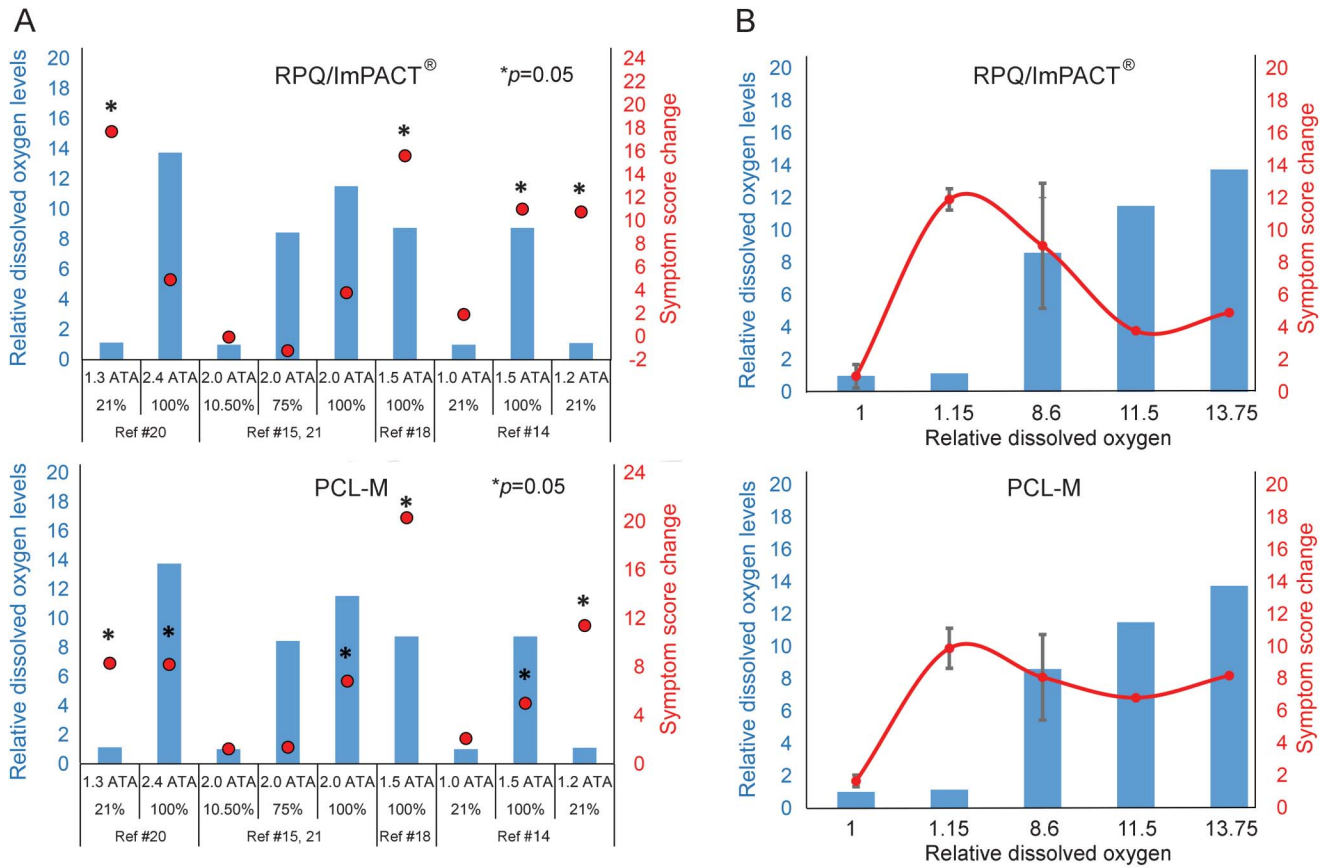
Dr. E. George Wolf,²⁰ lead author of the first published work of the DoD/VA-sponsored studies, clarified his position on his original conclusion¹³ and conceded that the controls used in his study might be active and bias the conclusions of the study. He noted the following:

Placebo effect in our previous reports has been considered as why there was no significant statistical difference in this study...However, both groups showed improvement in scores and thus a benefit. Given the studies demonstrating hydrostatic pressure effects and results of Boussi-Gross' crossover study, our design could be considered a treatment comparison vs a true sham with a therapeutic effect from both increased oxygen partial pressure and hydrostatic pressure. A Type II statistical error cannot be ruled out...There is a potential gain and no potential loss. The VA/Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients." At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.¹³

There is a substantial body of evidence that demonstrates the biological activity of pressurized air (see Biological effects of pressurized gases). The consistency of improvement affirms the therapeutic effect of HBOT on mTBI/PPCS (figure 1). Given the consistent improvement reported in recent clinical trials (a total of 5 out of 5 studies demonstrate a statistically significant improvement in one or both primary outcome measures posttreatment) and the excellent safety record of hyperbaric treatment, HBOT should be prescribed for mTBI/PPCS.

DISCUSSION Biological effects of pressurized gases. As mentioned earlier, we countered that it was incorrect

Figure 1 Changes in average symptom score (pre- vs post-HBOT) and dissolved oxygen in plasma



Results of the Department of Defense/Veterans Administration studies, the Army-sponsored studies, and the Harch et al.¹⁸ civilian study. (A, left column) Total points change in score values from baseline assessment tests in traumatic brain injury symptom scores (top) and the PTSD Checklist-Military outcome scores (bottom). Outcomes are grouped by publication source. (B, right column) Outcome values from the left graphs grouped by relative dissolved oxygen levels. 1 = 1.0 ATA, 21% O₂ equivalents (Miller et al.¹⁴ and Cifu et al.^{15,16}; N = 44). 1.15 = 1.2 and 1.3 ATA, 21% O₂ (Miller et al.¹⁴ and Wolf et al.²⁰; N = 49). 8.6 = 1.5 and 1.5 ATA, 100% O₂/2.0 ATA, 75% O₂ (Harch et al.¹⁸ Miller et al.¹⁴ Cifu et al.^{15,16}; N = 58). 11.5 = 2.0 ATA, 100% O₂ (Cifu et al.^{15,16}; N = 21). 13.75 = 2.4 ATA, 100% O₂ (Wolf et al.²⁰; N = 24). Error bars are standard deviation. Red dots are the average symptom scores. Blue bars are dissolved oxygen levels. HBOT = hyperbaric oxygen therapy; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; RPQ = Rivermead Post-Concussion Questionnaire.

when the DoD/VA/Army-sponsored studies utilized pressurized air as a control group (they labeled them sham comparators). The use of an air group was based on the assumption that pressures below 1.4 ATA and oxygen concentration of 21% O₂ would have minimal to no effect. The literature in experimental biology and preclinical animal models is extensive, and demonstrates that low-pressure pure oxygen or low-pressure medical grade air induce biologically measurable and therapeutic responses.

The clearest example to date that demonstrates that these gas/pressure combinations have a therapeutic effect on brain injury models is the article by Malek et al.²² They demonstrated that HBO (100% O₂) and HBA (21% O₂/79% N₂) were equivalent in protecting neurons after transient forebrain ischemia in the gerbil using 2.5 ATA. Gerbils were induced to undergo ischemia and then treated (HBO, HBA, or normobaric oxygen), not treated, or given a sham surgery without inducing ischemia. No

statistically significant difference between HBO and HBA was observed in neuronal protection; both were equally effective in protecting against neuronal loss when compared to the ischemic group. Malek et al. suspected that pressurized air had therapeutic potential and therefore compared all treatment groups against a sham surgical control. The role of a potential placebo effect was ruled out in this study and demonstrates the activity of HBO and HBA in a neurologic injury model.

HBA and low-pressure HBO (≤ 1.2 ATA) also have shown repeated biological effects in cell culture studies²³⁻²⁵ and clear differential effects when applying HBO (2.4 ATA, 21% O₂)²⁶ vs pressure alone (2.4 ATA, 8.8% O₂; 21% O₂ equivalent) or oxygen alone (1.0 ATA, 100% O₂). There appears to be a threshold of oxygen concentration that is required for producing a biological response when greater than atmospheric pressure is applied. This reliance on increased pressure to elicit a biological response appears to be cell type

independent.²⁷ These results suggest a combination of oxygen + pressure is critical to achieving a biological response, even with pressures that are thought to be trivial or noneffective. No systematic, in-depth analysis of the minimally effective oxygen concentration, coupled to increases (or decreases) in absolute pressure, have been undertaken in animal or cell culture studies. Although important to the understanding of potential mechanisms of action for HBOT and HBA, the current results should not be dismissed as a placebo or Hawthorne effect. Ideally, a dose-response curve with an animal model would help to delineate the observed effects of pressurized oxygen and nitrogen, establishing the rationale for a true sham.

Animal studies demonstrating the effects of a threshold level of oxygen + pressure are equally revealing in the areas of muscle injury repair in rats. Small increases in pressure ([1.25 ATA, 100% O₂] vs [1.0 ATA, 100% O₂])²⁸ induce accelerated repair. Changes in insulin/glucose response and muscle force twitch were observed in the pressure group (1.25 ATA, 36% O₂), but not in the pure oxygen group (1.0 ATA, 100% O₂).^{29,30} Furthermore, the protective effects of HBA (2.5 ATA, 21% O₂) on cerebral heatstroke³¹ only worked when pressure was applied. The notion that low-pressure pure oxygen or high-pressure air can be a sham is not supported by the cell culture and animal data. Furthermore, there are unresolved issues associated with tissue sensitivity and responses to changes in dissolved oxygen concentration in humans. What is good for wound healing at skin and skeletal muscle levels (which are hypoxia-tolerant) may not be the same for neural or cardiac tissue (which are hypoxia-sensitive).

One key question that remains in the hyperbaric medical literature is a unifying mechanism of action to carry out the observed effects of gases delivered at pressures greater than 1.0 ATA. As displayed in figure 2, levels of dissolved oxygen in plasma vary by pressure and the % oxygen levels in the breathed fraction. Breathing 100% O₂ at 1.0 ATA delivers far more dissolved oxygen than breathing air at 3.0 ATA of 21% O₂. Yet 100% O₂ at 1.0 ATA does not have the same effect for TBI or ischemic models of injury as 1.2 or 1.5 ATA of 21% O₂. A great deal of research and new thinking must be applied to understand what is really happening to explain the animal and clinical data we are seeing with HBA and HBO. The lack of an identifiable mechanism does not invalidate the observed effects.

Hyperbaric medicine has gone through a contentious history,³² with editorials characterizing hyperbaric medicine as “A therapy in search of diseases,”³³ editorial opinions discounting biological effects of pressurized air,^{34,35} and studies that assume little or no biological activity of a pressurized air “control.”^{14–16,36,37}

In all the published studies, patients with mTBI/PPCS improved from their baseline values in a measurable, consistent manner and in excess of what is seen with available local care for mTBI/PPCS.^{14,19} These improvements were consistent in 4 independent US-based studies and even with weighted averages applied, the results are large and significant (figure 3). The heterogeneous nature of a TBI should not bias the physician from overlooking the ability of HBO (or HBA) in assisting or accelerating repair of the brain. HBOT has accumulated a rather large body of evidence on the myriad biochemical, physiologic, and cellular effects that it can elicit^{38–40} to induce repair in the body.

It is important to remember that the improvements reported with the reviewed mTBI/PPCS trials occur years after medical consensus opinion believes that improvements of this magnitude can occur. When reviewing the published studies, one must accept that variable doses are being applied and no validated sham controls are present. This fundamentally shifts the interpretation of data in these studies.

The criteria established by the editors of *Neurology*^{41–43} state the following for B-level evidence: “Level B rating requires at least 1 Class I study or 2 consistent Class II studies.” The current literature presents at least B-level evidence for the use of HBOT to treat the symptoms of mTBI/PPCS and PTSD secondary to an mTBI:

1. Four Class I studies on the use of HBOT on mTBI/PPCS show a positive outcome when baseline and posttreatment outcome measures are compared objectively and without assumptions of inactivity from the control groups.

Figure 2 Levels of dissolved oxygen in plasma (mL O₂/L plasma) at varying oxygen concentrations and pressures of hyperbaric air and oxygen

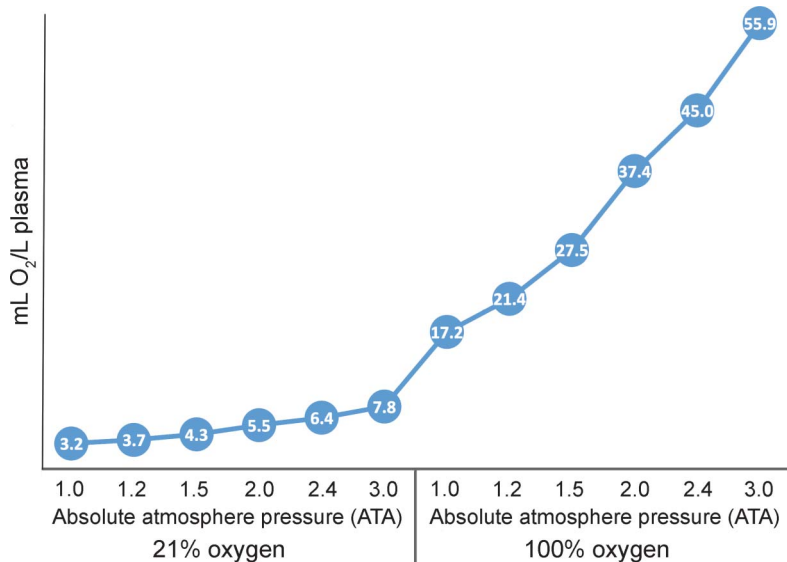
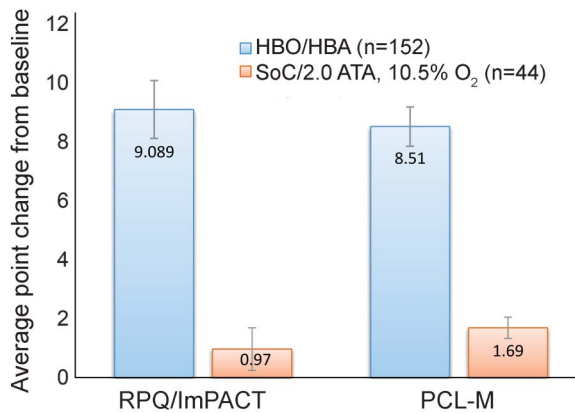


Figure 3 Weighted aggregated averages of the Department of Defense/ Veterans Administration, Army, and civilian studies



Hyperbaric oxygen (HBO) and hyperbaric air (HBA) at 1.2–2.4 ATA produce improvements that are superior to the combined standard of care (SoC) or the 21% oxygen equivalent concentration control (10.5% oxygen at 2.0 ATA) values. Error bars are SD. ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; PCL-M = PTSD Checklist-Military; RPQ = Rivermead Post-Concussion Questionnaire.

- a. The studies by Miller et al.,¹⁴ Cifu et al.,^{15,16} Wolf et al.,²⁰ and Boussi-Gross et al.¹⁹ meet all the criteria for Class I evidence (neurology.org/site/misc/TableClassificationScheme.pdf).
2. One Class III study on the use of HBOT on mTBI/PPCS shows a positive outcome.
 - a. The study by Harch et al.¹⁸ used well-defined natural history records, with patients serving as their own controls. Pretreatment and posttreatment testing were independently assessed and derived by objective outcome measures.¹⁸ All participants experienced statistically significant symptom improvements for TBI and PTSD measures.

It would be a great loss to clinical medicine to ignore the large body of evidence collected so far that consistently concludes that HBO is effective in treating brain injuries.

The need for further studies is an often-made statement in clinical research, but if further research is to be attempted in the area of HBOT for neurologic injuries, the use of pressurized shams should be avoided, until such a time that a true sham has been identified. Furthermore, HBOT should be made available as an adjunct to standard of care for mTBI/PPCS treatment, as clinical application can allow for information capture in a national database and treatment parameters refined by application and experience.

The placebo effect and Hawthorne effects purported to exist in the studies must be addressed. The ongoing debate and lack of clear information as to what may constitute an effective sham must account for both pressure and oxygen levels (nitrogen, as well). An adequate sham group in a clinical trial would,

at minimum, be required to enter a hyperbaric chamber, spend an equivalent time as the treatment group inside the chamber, breathe room air, and not undergo pressurization. Ensuring a double-blind becomes difficult, but not impossible to achieve with this type of sham.

The Hawthorne effect may play a role in the outcomes of the published clinical trials in HBOT, but participation in a validated sham group would help control for that effect. If shams are not to be used in future HBOT trials, it is recommended that study participants randomized to the control group undergo the same treatment at the hands of the clinic as HBOT interventions group sans exposure to a chamber. This would require that control participants attend a study site at a fixed time during the day and perform the same tasks as the HBOT treatment participants. In most cases, active arm participants are allowed to watch movies, read, or listen to music in either a multiplace or monoplace chamber. Having the same activities for Hawthorne control group as the HBOT treatment group should suffice. If the improvement attributed to a placebo or Hawthorne effect is significant, which some researchers say is the case, it is surprising that no one appears to have endorsed this as a treatment for TBI or attempted to replicate the outcome in a parallel study.

Finally, a Food and Drug Administration sanction should be sought for future studies and the NIH should be strongly encouraged to revisit HBO as a potential therapy and provide funding for definitive phase III trials, under the guidance and oversight of national and international monitors. The implications of HBOT for neurologic recovery and repair have far-reaching consequences in the medical fields of neurology and rehabilitation medicine and for public health in general. Important in this proposed phase III study for mTBI/PPCS is the need to properly diagnose study participants and use both objective and subjective pre- and post-baseline measures.

For objective measures, at a minimum PET or SPECT would provide a clear picture of metabolic and blood flow changes to the brain of injured subjects. MRI technologies, such as diffusion tensor imaging and functional MRI, would be ideal, but expensive and limited by the number of machines of enough field strength to provide imaging. Subjective measures are an important tool for assessing clinically meaningful changes in study subjects. The use of symptom questionnaires that are specific to mTBI/PPCS, general health and attitude surveys, and cognitive tests that measure established neurologic deficits in this population should be used. Computerized assessment systems provide unbiased, timed, and altered forms for repeat testing of this population.

Furthermore, a national database should be created for physicians and hyperbaric clinics to deposit treatment data for individuals who are using HBOT for mTBI/PPCS. The current loss of data on outcomes of self-paying or pro bono treatments needs to be captured with an organized and standardized system of data gathering. People are using this therapy and it is a tremendous waste of resources not to derive meaningful health outcome information from this population.

There is sufficient evidence for the safety and preliminary efficacy data from clinical studies to support the use of HBOT in mTBI/PPCS. The reported positive outcomes and the durability of those outcomes has been demonstrated at 6 months post HBOT treatment.¹⁸ Given the current policy by Tricare and the VA to allow physicians to prescribe drugs or therapies in an off-label manner for mTBI/PPCS management and reimburse for the treatment, it is past time that HBOT be given the same opportunity. This is now an issue of policy modification and reimbursement, not an issue of scientific proof or preliminary clinical efficacy.

AUTHOR CONTRIBUTIONS

Dr. Figueroa developed the review concept and design, collected the data, analyzed and interpreted the data, and supervised the study. Dr. Wright provided critical revisions of the manuscript and important intellectual content and provided additional interpretation to the data analysis. Both authors contributed time, funds, and effort in preparing this manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

X. Figueroa is a scientific and technical consultant for Nativis, Inc. (60%), ENG³ (10%), and Cytokinetics (15%). He volunteers his time as the President of the Brain Health & Healing Foundation and writes for the Foundation's blog. J. Wright is an employee of Swedish Medical Center (Edmonds), Wound Healing and Hyperbarics, where he performs in a clinical practice (100%) and bills for his procedures. He volunteers his time as a member of the Science Advisory Board for the Brain Health & Healing Foundation. Go to Neurology.org for full disclosures.

Received November 4, 2015. Accepted in final form May 9, 2016.

REFERENCES

1. Stoller KP. Hyperbaric oxygen therapy (1.5 ATA) in treating sports related TBI/CTE: two case reports. *Med Gas Res* 2011;1:17.
2. Lv LQ, Hou LJ, Yu MK, Ding XH, Qi XQ, Lu YC. Hyperbaric oxygen therapy in the management of paroxysmal sympathetic hyperactivity after severe traumatic brain injury: a report of 6 cases. *Arch Phys Med Rehabil* 2011;92:1515–1518.
3. Wright JK, Zant E, Groom K, Schlegel RE, Gilliland K. Case report: treatment of mild traumatic brain injury with hyperbaric oxygen. *Undersea Hyperb Med* 2009;36:391–399.
4. Harch PG, Fogarty EF, 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;2:6538.

5. 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;253:94–105.
6. Golden Z, Golden CJ, Neubauer RA. Improving neuropsychological function after chronic brain injury with hyperbaric oxygen. *Disabil Rehabil* 2006;28:1379–1386.
7. Ren H, Wang W, Ge Z, Zhang J. Clinical, brain electric earth map, endothelin and transcranial ultrasonic Doppler findings after hyperbaric oxygen treatment for severe brain injury. *Chin Med J* 2001;114:387–390.
8. Ren H, Wang W, Ge Z. Glasgow Coma Scale, brain electric activity mapping and Glasgow Outcome Scale after hyperbaric oxygen treatment of severe brain injury. *Chin J Traumatol* 2001;4:239–241.
9. Lin JW, Tsai JT, Lee LM, et al. Effect of hyperbaric oxygen on patients with traumatic brain injury. *Acta Neurochir Suppl* 2008;101:145–149.
10. Sahni T, Jain M, Prasad R, Sogani SK, Singh VP. Use of hyperbaric oxygen in traumatic brain injury: retrospective analysis of data of 20 patients treated at a tertiary care centre. *Br J Neurosurg* 2012;26:202–207.
11. Nakamura T, Kuroda Y, Yamashita S, et al. Hyperbaric oxygen therapy for consciousness disturbance following head injury in subacute phase. *Acta Neurochir Suppl* 2008;102:21–24.
12. Neubauer RA, Gottlieb SF. Hyperbaric oxygen for brain injury. *J Neurosurg* 1993;78:687–688.
13. Wolf EG, Baugh LM, Schubert Kabban CM, Richards MF, Prye J. Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial. *Underwater Hyperb Med* 2015;42:313–332.
14. 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;175:43–52.
15. Cifu DX, Walker WC, West SL, et al. Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes. *Ann Neurol* 2014;75:277–286.
16. Cifu DX, Hart BB, West SL, Walker W, Carne W. The effect of hyperbaric oxygen on persistent postconcussion symptoms. *J Head Trauma Rehabil* 2014;29:11–20.
17. Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O. Hyperbaric side effects in a traumatic brain injury randomized clinical trial. *Undersea Hyperb Med* 2012;39:1075–1082.
18. 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;29:168–185.
19. 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:e79995.
20. 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;29:2606–2612.
21. Hoge CW, Jonas WB. The ritual of hyperbaric oxygen and lessons for the treatment of persistent postconcussion symptoms in military personnel. *JAMA Intern Med* 2014;175:53–54.

22. Malek M, Duszczyk M, Zyszkowski M, Ziembowicz A, Salinska E. Hyperbaric oxygen and hyperbaric air treatment result in comparable neuronal death reduction and improved behavioral outcome after transient forebrain ischemia in the gerbil. *Exp Brain Res* 2013;224:1–14.
23. Acevedo AD, Bowser SS, Gerritsen ME, Bizios R. Morphological and proliferative responses of endothelial cells to hydrostatic pressure: role of fibroblast growth factor. *J Cell Physiol* 1993;157:603–614.
24. Tokunaga O, Fan JL, Watanabe T. Atherosclerosis and endothelium: part II: properties of aortic endothelial and smooth muscle cells cultured at various ambient pressures. *Acta Pathol Jpn* 1989;39:356–362.
25. Tokunaga O, Watanabe T. Properties of endothelial cell and smooth muscle cell cultured in ambient pressure. *In Vitro Cell Dev Biol* 1987;23:528–534.
26. Al Hadi H, Smerdon GR, Fox SW. Hyperbaric oxygen therapy accelerates osteoblast differentiation and promotes bone formation. *J Dent* 2015;43:382–388.
27. Oh S, Lee E, Lee J, Lim Y, Kim J, Woo S. Comparison of the effects of 40% oxygen and two atmospheric absolute air pressure conditions on stress-induced premature senescence of normal human diploid fibroblasts. *Cell Stress Chaperones* 2008;13:447–458.
28. 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:e115685.
29. Yasuda K, Adachi T, Gu N, et al. Effects of hyperbaric exposure with high oxygen concentration on glucose and insulin levels and skeletal muscle-fiber properties in diabetic rats. *Muscle Nerve* 2007;35:337–343.
30. Matsumoto A, Nagatomo F, Yasuda K, Tsuda K, Ishihara A. Hyperbaric exposure with high oxygen concentration improves altered fiber types in the plantaris muscle of diabetic Goto-Kakizaki rats. *J Physiol Sci* 2007;57:133–136.
31. Tai PA, Chang CK, Niu KC, Lin MT, Chiu WT, Lin JW. Attenuation of heat-induced hypothalamic ischemia, inflammation, and damage by hyperbaric oxygen in rats. *J Neurotrauma* Epub 2010 Jun 25.
32. Moon RE, Camporesi EM. Hyperbaric oxygen therapy: from the nineteenth to the twenty-first century. *Respir Care Clin N Am* 1999;5:1–5.
33. Gabb G, Robin ED. Hyperbaric oxygen: a therapy in search of diseases. *Chest* 1987;92:1074–1082.
34. Mitchell SJ, Bennett MH. Unestablished indications for hyperbaric oxygen therapy. *Diving Hyperb Med* 2014;44:228–234.
35. Bennett MH. Hyperbaric medicine and the placebo effect. *Diving Hyperb Med* 2014;44:235–240.
36. Anderson DC, Bottini AG, Jagiella WM, et al. A pilot study of hyperbaric oxygen in the treatment of human stroke. *Stroke* 1991;22:1137–1142.
37. Rusyniak DE, Kirk MA, May JD, et al. Hyperbaric oxygen therapy in acute ischemic stroke: results of the hyperbaric oxygen in acute ischemic stroke trial pilot study. *Stroke* 2003;34:571–574.
38. Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. *Med Gas Res* 2015;5:9.
39. Harch PG. The genetically modulated healing effects of hyperbaric oxygen therapy. *Altern Ther Health Med* 2015;21:46–55.
40. Figueroa XA, Wright JK. Clinical results in brain injury trials using HBO2 therapy: another perspective. *Undersea Hyperb Med J* 2015;42:19.
41. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. *Neurology* 2008;71:1634–1638.
42. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. *Neurology* 2008;71:1639–1643.
43. Gross RA, Johnston KC. Levels of evidence: taking neurology to the next level. *Neurology* 2009;72:8–10.