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Letter to the Editor

Hyperbaric Oxygen Therapy for Post-Concussion Syndrome: Contradictory Conclusions from a Study Mischaracterized as Sham-Controlled

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Dear Editor,

The recent study by Wolf and associates[1] has affirmed the effectiveness of hyperbaric (oxygen) therapy in the treatment of patients with mild traumatic brain injury (mTBI)/post-concussion syndrome (PCS) and post-traumatic stress disorder (PTSD). This affirmation emerges from analysis of the study data, rather than from the study's stated conclusions. Mischaracterized as a sham-controlled (placebo implied) design, the study errs in concluding that "HBO_2 at 2.4 ATA pressure had no effect on post-concussive symptoms after mild TBI." A reconsideration of the science of hyperbaric therapy reveals that the study by Wolf and colleagues[1] is neither a sham nor placebo-controlled study. Rather, it is a Phase II study of two composite doses of hyperbaric therapy that demonstrated significant improvements in PCS and PTSD symptoms at the 2.4 atmospheres absolute (ATA) pure oxygen dose as well as the low-pressure 1.3 ATA air/oxygen dose.

Hyperbaric (oxygen) therapy (HBOT) is a combination product of increased pressure and increased pressure of oxygen above ambient atmospheric pressure, according to scientific principles and current Food and Drug Administration understanding. Although traditionally misdefined as a treatment for diseases based on the increased oxygen component alone (> 1.4 ATA oxygen),[2] it is a treatment with hyperbaric pressure and hyperoxia for disease processes[2,3] whose primary targets are oxygen and pressure sensitive genes.[4–6]

Evidence for this dual component nature of hyperbaric therapy is found in the 351-year history of hyperbaric air therapy[7] and the recent 60-year history of animal, human tissue, and human experiments that have documented biological effects of pressure, especially in the micropressure range[8,9] of the Wolf and coworkers[1] "sham" control group and the control groups of the Department of Defense (DoD) HBOT TBI studies.[10] Examples of this literature are listed in Tables 1 and 2.[11–28] Pressures from 1.21–1.26 ATA delivered to human[29–31] and 1.0015–1.015 ATA to animal endothelial cells,[32] and 1.10 and 1.20 ATA to human platelets[33,34] for 15 min or longer have caused the elaboration or suppression of vasoactive substances,[29–31] and the elaboration of growth factors,[32] inflammatory mediators,[33] oxidation products,[34] and cell proliferation.[32] This literature and biological effects from a 1-min exposure to 1.09 ATA or 3 min at 1.04 ATA[17] inform the symptomatic improvements noted in the Wolf and associates[1] "sham" group, as do benefits of hyperbaric air on spinal function and PTSD in spinal cord injured veterans during a SCUBA diving training course.[28]

To meet the definition of a true sham,[35] any controlled experiment to test HBOT must omit in its control groups the active ingredients of increased pressure and hyperoxia. The Wolf and colleagues[1] "sham" control group does neither; rather, it includes both. The "sham" control group is exposed to 1.3/1.2 ATA of air, which is a 20–30% increase in pressure and 28–43% increase in plasma oxygen[36] over sea level plasma oxygen and a slightly greater increase over San Antonio (hyperbaric treatment site) atmospheric pressure.[37] Because pressure and hyperoxia are non-inert—i.e., are biologically active—the Wolf and coworkers[1] "sham" control group cannot test for placebo effects; placebo/placebo response is defined as "The effect that an inactive or inert substance has on a clinical condition."[38] Wolf and associates[1] allude to possible bioactivity of the control group, but the lack of discussion indicates a lack of appreciation that the presence of hyperoxia and pressure negate Wolf and colleagues[1] characterization as a "sham" control group.

Restating the design of the Wolf and coworkers[1] study, it is a Phase II comparative dosing study of two composite doses of hyperbaric therapy (four actual doses), compressed air (low dose increased pressure and increased oxygen), and compressed oxygen (high dose pressure and high dose oxygen). Both doses were efficacious in the treatment of mTBI PCS and PTSD. The PTSD data demonstrated 18% and 22% reductions in the PCL-M (interpolated from the Figure 1 graph in Wolf and colleagues[1]) in the HBOT and "sham" groups, respectively, after 30 2 h treatments. These reductions compared favorably with five other therapies/six studies for PTSD[39–44] that used the PCL-M (6–45% reductions).

The PCS ImPACT data were similarly significantly improved in both groups, but it is the disparity in component and pattern change on the ImPACT results for the two groups that underscore the dual dose design of the study and efficacy of these two doses: 10 IMPACT scores significantly improved in the low dose group compared with 2 in the high dose group. For all 22 items of the ImPACT, 20 improved, 1 was unchanged, and 1 was worse in the

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Table 1. In vitro and In vivo Studies on Hyperbaric (Pressure and Oxygen) Effects

Study	*Year*	*Model:* In Vivo (IV), In Vitro (IVT)	*Animal/human*	*Ambient gas*
1. Cunningham, O.J.[11]	1900–1929	Multiple medical disorders	Human	Air
2. Dowell, R.T.[12]	1978	Aortic constriction (IV)	Rat-neonate and adult	Air
3. Hishikawa, K.[13]	1994	Vascular smooth muscle cells, IVT	Rat	Helium
4. Mattana, J.[14]	1995	Mesangial (renal) cells (IVT)	Rat	95% air, 5% CO_2
5. Teiger, E.[15]	1996	Aortic constriction (IV)	Rat	Air
6. Kramer, M.R.[16]	1998	COPD-pulmonary function	Humans	Air
7. Kawata, Y.[17]	1998	Mesangial (renal) cells (IVT)	Rat	Air
8. Macdonald, A.G.-review[9]	1999	Wide range of IV and IVT	Bacteria, insect, nematode, animal, human	95% air, 100% air, helium
9. Agar, A.[18]	2000	Neuroblastoma (IVT), glaucoma model	Rat	95% air, 5% CO_2
10. Dean, J.B.[19]	2000	Brain stem neurons (IVT)	Rat	Air, helium
11. Heal, R.D.[20]	2001	Dorsal root ganglion neurons (IVT)	Rat	95% air, 5% CO_2
12. Collet, J.P.[21]	2001	Cerebral palsy (IV)	Human-children	Air, 100% oxygen
13. Yu, H.A.I.[22]	2002	Subacute hypoxic-ischemia brain injury (IV)	Rat	Air, 100% oxygen
14. Heuser, G.[23]	2002	Chronic toxic encephalopathy or autism (IV)	Human-adults and children	24% oxygen
15. Kazantseva, N.V.[24]	2002	Cerebrovascular injury, epilepsy, migraine (IV)	Human adults	30%, 40%, and 100% oxygen
16. Rusyniak, D.E.[25]	2003	Acute stroke	Human-adults	100% oxygen
17. Stanley, A.C.[26]	2005	Fibroblast wound-healing (IVT)	Human neonatal fibroblasts	94% air, 6% CO_2
18. Rossignol, D.A.[27]	2009	Autism	Human-children	Air, 24% oxygen
19. Kaplin, A.[28]	2011	Spinal cord injury and PTSD	Human-veterans	Air

COPD, chronic obstructive pulmonary disease; PTSD, post-traumatic stress disorder.

low dose group, while 11 improved, 3 were unchanged, and 8 were worse in the high dose group (Table 1 in Wolf and associates[1]). The pattern of composite ImPACT scores over the course of the study is also different for the two groups (Figure 2 in Wolf and coworkers[1]). Subjects in the low dose group experienced initial deterioration then steady improvement until the end of the study while the high dose group showed improvement then a steady reversal of benefit to near baseline, followed by rebound improvement 6 weeks post-treatment.

This sinusoidal trajectory in the high dose group suggests a differential dosing effect and possibly an overdose response with partial recovery after removal of the high dose, and is consistent with the worsening of eight scores in this group. It is also consistent with a phenomenon previously described and documented in multiple cases of HBOT treatment of chronic cerebral disorders.[45]

Since the initial submission of this Letter to the Editor, Wolf and colleagues[1] have now confirmed this overdosing effect on PCS symptoms in the 2.4 ATA group in a subset analysis presented on June 14, 2013.[46] This demonstration of low dose effectiveness and progressive high dose overdosing is also evident in other animal and clinical studies.[25,47,48]

Wolf and associates[1] list multiple possibilities for the improvements in PCS and PTSD, including ''placebo, Hawthorne effect, the natural resolution of symptoms over time,…exposure to sham-control partial pressures of oxygen and nitrogen,…and change in living environment…and daily routine.'' While 30 chamber experiences and change in living environment and daily routine are theoretical placebo contributions, the myriad standard clinical pressure/hyperoxia[2] and micropressure-induced biological effects demonstrated in both animal and human studies[8,9] and Tables 1 and 2 suggest that placebo is not the majority effect.

At the same time, placebo effects were also present in all six of the aforementioned PTSD/PCL-M studies. Hawthorne effect is also theoretically possible, but the foundation/proofing of the Hawthorne effect has been undermined by re-evaluation of the initial data set.[49] Symptoms in veterans with TBI and PTSD, in fact, do not resolve over time, as acknowledged by Wolf and coworkers[1] in their conclusion ''improved more than would be expected greater than 6 months after mTBI,'' and reports on persistent care and even worsening of condition over time in the Veterans Affairs system.[50,51]

All of the explanations by Wolf and colleagues,[1] however, do not explain the disparity in component and pattern change in the ImPACT data and transient overdose effect in the high dose oxygen group. If placebo, Hawthorne effect, and other non-biological etiologies are causally entertained, why wouldn't the component and pattern changes be identical in the two groups? The last choice, effects of increased partial pressures of oxygen and nitrogen, seems most plausible as the dominant etiology for the statistically significant improvements in both groups, but it is not necessarily nitrogen pressure, but pressure, per se, that is involved. Wolf and associates[1] state, however, ''…it seems very unlikely such a minimal dose of oxygen and nitrogen could influence brain function favorably.'' The preceding argument and studies in Table 1 and 2 suggest the opposite.

In conclusion, the study by Wolf and colleagues[1] is a non-sham/non-placebo/non-controlled Phase II two composite dose study of hyperbaric therapy (hyperbaric air and hyperbaric oxygen) in U.S. veterans with PCS from mTBI with or without PTSD. The study demonstrated significant net improvements in PCS and PTSD symptoms with both doses of hyperbaric therapy, improvements that are similar in magnitude to other therapies for PTSD and greater than would be expected for PTSD and PCS over time without treatment based on the natural history of the diseases and published persistence rates in veterans.[50,51] Their results are thus comparatively effective to other existing therapies for PTSD and possibly PCS of mTBI.

Table 2. Continuation of Table 1 In vitro and in Vivo Studies on Hyperbaric (Pressure and Oxygen) Effects

Study	*Oxygen pressure (ATA): Control:experimental*	*Total pressure (ATA): Control:experimental*	*Duration/# Rxs*	*Effect*
1.	No controls:0.281–0.496	No controls: average1.34–2.36 ATA, max 3 ATA	2–3 hours up to days. Multiple treatments	Generally, improvement in clinical and laboratory parameters
2.	0.129:0.129 (arterial oxygen partial pressure)	1.103–1.163: 1.150–1.217	2,3,4,5 weeks	Cardiac myocyte and non-myocyte proliferation
3.	0.205:0.205	1.000:1.053, 1.105, 1.158	24 and 48 h	Increased cell proliferation and DNA synthesis; process begins w/i 30s press.
4.	0.23:0.237, not measured for 2nd pressure	1.000:1.053–1.066 and 1.066–1.079	1 or 7 days	Decreased cell number and increased matrix collagen (MC) at 7d. Dose-response for MC.
5.	0.129:0.129 (arterial oxygen partial pressure)	Approximately same as #1; same model	1,2,4,7,15,30 days	Increased apoptosis of cardiac myocytes by 1 day, peak at 4 days
6.	No controls (pre/post):0.221	Pre: 0.912 Post: 1.0526	21 days	Improved arterial oxygen and exercise capacity.
7.	0.270:0.270	1.000:1.039, 1.066, 1.092, 1.118	1–30 minutes, 12, 24, 48 hours	Enzyme activation w/i 1 min @ 1.092 ATA, gene expression/ proliferation post 12 h and 24 h exposure
8.	0.199:0.251	1.000:1.010–1.260	Few sec-days	Wide range of biological effects
9.	0.222:0.222	1.000:1.131	2 h	Increased apoptosis
10.	0.950:2.352–3.332	1.000:1.000–4.000	5–15 min	Differential effects of pressure and oxygen on firing rate
11.	0.199:0.599	1.000:3.000	8 min 20 sec	Suppression of firing rate
12.	0.273:1.750	1.300:1.750	60 minutes/d × 40 d	Both groups: Significant improvements in motor and cognition
13.	0.250:0.625, 2.50	1.000:2.500	60 minday × 10 days	Increased bFGF in hyperbaric air, increased bFGF and bFGF mRNA in HBO
14.	No control: 0.312	No control: 1.30	1 h/day × 10 days	Improved blood flow on SPECT brain imaging
15.	0.300:0.330, 0.480, 1.500	1.000:1.100, 1.200, 1.500	15–20m? × 5: 15–20m × 4–10, 20 m × 1 or 4–5, 60 m × 5	Improvement symptoms, EEG, blood flow, vital signs, biochemical params. < 1.5 ATA
16.	1.14:2.50	1.14:2.50	1 h	Better outcome in the low dose group
17.	0.194:0.205, 0.213, 0.229	1.000:1.039, 1.079, 1.158	12–18 h	Delayed wound healing and less proliferating cell nuclear antigen
18.	0.216; 0.312	1.03:1.30	1 h/day × 40 days	Clinical improvement
19.	SCUBA course	Likely < 3 ATA	Likely < 1 h	Improved spinal cord function and PTSD

ATA, atmospheres absolute; bFGF, basic fibroblast growth factor; HBO, hyperbaric oxygen; EEG, electroencephalography; PTSD, post-traumatic stress disorder.

If further evidence for the efficacy of hyperbaric therapy in mTBI PCS and PTSD is deemed necessary, as alternatives to the ''pivotal'' trial,[10] and in light of nearly $1 billion dollars of research and development money already spent by the Department of Defense (DoD) on research seeking effective treatments for TBI and PTSD, this author would suggest two options: (1) Abandoning the pursuit of a ''sham'' hyperbaric control group and prioritizing the data from the wait-list group in the DoD HOPP study[10] (Wolf and coworkers[1] mention a wait-list group in their recommendations for future studies). This option is based on the physical impossibility of controlling for a chamber experience because of the inability to control for pressure (no method to duplicate middle ear pressure changes without placement of pressure equalization tubes and no commercially available mechanisms to duplicate adiabatic heating and cooling on compression and decompression). Continued attempts at a ''sham'' pressure control group will only further confuse the scientific and lay community; and (2) an economical Civilian/DoD/Veterans Affairs (VA) off-label networked hyperbaric treatment program using a Medicare-like Coverage with Evidence Development[52] pathway. The safety of HBOT 1.5 and even higher doses is not in issue; hyperbaric oxygen therapy in mTBI PCS/PTSD has satisfied one of the cardinal rules of medicine, ''First, Do No Harm.'' The Coverage with Evidence pathway would allow the DoD and VA to immediately begin treating active military and veteran casualties with hyperbaric therapy in both military and civilian clinics/hospitals such that this health and quality of life improving therapy can be delivered without further delay to the hundreds of thousands of injured PCS/PTSD casualties and veterans now in need.

Author Disclosure Statement

Dr. Harch owns a small consulting company, Harch Hyperbarics, Inc., and is president of a non-profit corporation, The International Hyperbaric Medical Foundation (IHMF). He derives no income, salary, or benefits from the IHMF.

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