The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms

David X. Cifu, MD; Brett B. Hart, MD; Steven L. West, PhD; William Walker, MD; William Carne, PhD

Background: The high incidence of persistent postconcussion symptoms in service members with combat-related mild traumatic brain injury has prompted research in the use of hyperbaric oxygen (HBO_2) for management. **Objective:** The effects of HBO_2 on persistent postconcussion symptoms in 60 military service members with at least 1 combat-related mild traumatic brain injury were examined in a single-center, double-blind, randomized, sham-controlled, prospective trial at the Naval Medicine Operational Training Center at Naval Air Station Pensacola. **Methods:** Over a 10-week period, subjects received a series of 40, once-daily, hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA). During each session, subjects breathed 1 of 3 preassigned oxygen fractions (10.5%, 75%, or 100%) for 60 minutes, resulting in an oxygen exposure equivalent to breathing surface air, 100% oxygen at 1.5 ATA, or 100% oxygen at 2.0 ATA, respectively. Individual, subscale and total item responses on the Rivermead Postconcussion Symptom Questionnaire and individual and total Posttraumatic Disorder Checklist–Military Version were measured just prior to intervention and immediately postintervention. **Results:** Between-group testing of pre- and postintervention means revealed no significant differences on individual or total scores on the Posttraumatic Disorder Checklist–Military Version or Rivermead Postconcussion Symptom Questionnaire, demonstrating a successful randomization and no significant main effect for HBO_2 at 1.5 or 2.0 ATA equivalent compared with the sham compression. Within-group testing of pre- and postintervention means revealed significant differences on several individual items for each group and difference in the Posttraumatic Disorder Checklist–Military Version total score for the 2.0 ATA HBO_2 group. **Discussion:** The primary analyses of between group differences found no evidence of efficacy for HBO_2. The scattered within group differences are threatened by Type 2 errors and could be explained by nonspecific effects. **Conclusion:** This study demonstrated that HBO_2 at either 1.5 or 2.0 ATA equivalent had no effect on postconcussion symptoms after mild traumatic brain injury when compared with sham compression. **Key words:** *hyperbaric oxygen therapy*, *postconcussion syndrome*, *traumatic brain injury*

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Funding was provided for the primary study by a Defense Advanced Research Projects Agency grant (N66001-09-2-206), US Navy Bureau of Medicine and Surgery for contract funding temporary duty requirements, and the US Army Medical Materiel Development Activity for end-of-study contract funding. Dr Carne's and Dr Walker's efforts were additionally supported through a contract from the Defense and Veterans Brain Injury Center. The funding sources had no role in the study design, analysis, interpretation of the data, the writing of the paper, or the decision to submit the paper for publication.

The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs, Department of Defense, or the US government.

The authors recognize and thank Ms Sheila Galvin, Traumatic Brain Injury Program Coordinator for the Wounded Warrior Regiment USMC, for her superb service in coordinating participant requirements; Ms Karen Guenther and the Injured Marine Semper Fi Fund, for transportation support for participants; Dr Jason Cromar, USAFSAM, for coordinating the protocol; the members of the Naval Aerospace Medicine Institute Hyperbaric Medicine Department, for supporting the 705 chamber dives and 139 man days of "bottom time" needed to complete this project; and Dr R. Scott Miller, US Army Medical Material Development Activity, Ft Detrick, Maryland, for manuscript review.

The authors declare no conflicts of interest.

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DOI: 10.1097/HTR.0b013e3182a6aaf0

WITH the onset of the Afghanistan and Iraq wars in October 2001, the US Departments of Defense (DoD) and Veterans Affairs (VA) have established a worldwide system of care to assess and manage the significant numbers of service members (SMs) and Veterans who have sustained mild traumatic brain injury (mTBI).[1] Aggregated screening data of all Operation Enduring Freedom (Afghanistan War) and Operation Iraqi Freedom (Iraq War) Veterans enrolled in the VA system of care through 2011 reveal that 9.6% experienced at least 1 mTBI during their deployments.[2] Of note, more than 90% of these individuals have at least 1 concomitant secondary diagnosis (eg, posttraumatic

stress disorder [PTSD], pain) that may confound both the clinical presentation and subsequent treatment.[2,3] This condition has been labeled postdeployment multisymptom disorder,[4] or more commonly postdeployment syndrome,[5] and may be one of the reasons for the higher rate of persistent postconcussion syndrome (PPCS) in military personnel than in civilian individuals.[3] The broad range and high frequency of various symptoms are the clinical hallmarks of these syndromes. In addition, many in the military have had repetitive blast exposures, potentially with associated head trauma and associated cumulative brain injury, that may further complicate symptom attribution and recovery.[6]

In an effort to evaluate the effectiveness of innovative treatment options for the array of symptoms seen with PPCS in US combatants, the DoD and VA have developed an initiative involving 3 ongoing independent, randomized, blinded trials to assess the utility of hyperbaric oxygen (HBO_2).[7] Together, these complementary investigations objectively study the effect on symptoms of a range of hyperbaric exposures on military and Veteran populations. The administration of HBO_2 involves breathing high levels of oxygen, usually 100%, at an increased pressure at least 1.4 times greater than the atmospheric absolute pressure at sea level (1 atmospheres absolute or ATA, which is equivalent to 760 mm Hg partial pressure of oxygen).[8] The partial pressure of oxygen will increase proportionally with an increase in the hyperbaric chamber compression pressure, consequently the intent of HBO_2 is to increase the oxygenation of the patient's blood and tissues to supraphysiologic levels as a stimulus to cellular growth and repair. The use of HBO_2 for treating TBI is based on the still unproven theory that functionally retrievable neurons, adjacent to severely damaged or dead neurons, exposed to HBO_2 may return to normal function or near normal function by reactivating metabolic or electrical pathways. Other possible mechanisms of benefit to TBI patients include stem cell mobilization to sites of injury, immunomodulation, and impact on fundamental neurotransmitters such as nitric oxide.[9] While these theories hold promise for future identification of those patients most likely to respond, in practical terms, symptom improvement remains the current metric for a positive therapeutic outcome.[7]

To date, the evidence for efficacy of HBO_2 in TBI is inconclusive. Randomized trials support the use of HBO_2 to improve survival after acute, severe TBI; however, there is no appreciable effect in functional outcomes.[10,11] Primarily anecdotal evidence exists to support HBO_2 for chronic TBI (ie, >3 months postevent), and the only published randomized clinical trial investigating HBO_2 for postconcussion syndrome demonstrated no effect.[9]

A typical HBO_2 clinical treatment uses oxygen at 2.0 to 3.0 ATA for the duration of 90 to 120 minutes; however, individualization based on diagnosis and patient symptoms has been advocated,[8] and anecdotal evidence exists to support efficacy in TBI at lower dosages (1.5 ATA).[10,12,13] A randomized, controlled trial using 2.4 ATA HBO_2 exposure compared with sham (room air at 1.3 ATA) failed to demonstrate any differences in symptoms in SMs with PPCS.[9] Given these results and the anecdotal reports of efficacy at lower, potentially safer pressures, the second phase of the DoD-VA research initiative focused on the effect of 1.5 and 2.0 ATA equivalent HBO_2 dosing. To this end, this investigation examined the effects of HBO_2 exposure on a population of active-duty SMs with PPCS following combat-related mTBI in a 3-arm, randomized, blinded, sham-controlled trial.

MATERIALS AND METHODS

Commencing in 2009, the Defense Advanced Research Projects Agency and the US Navy Bureau of Medicine and Surgery (as part of the DoD-VA collaborative research program) sponsored this single-center, 3-arm, randomized, blinded, sham-controlled trial of HBO_2 exposure on symptomatic mTBI patients. The logistics and challenges of double-blinding hyperbaric chamber interventions have been described previously.[14] This study received appropriate institutional review board and governmental approvals. Sixty-one active-duty military SMs with PPCS were recruited from US military bases. Inclusion criteria were TBI specialist–confirmed diagnosis of mTBI based on the DoD definition of TBI (Health Affairs 2007),[15] postconcussive symptoms from mTBI for at least 3 months, injury occurrence in the past 3 years, psychiatric status (if any) stable for 2 months, stable psychotropic medication history for at least 1 month, and ability to use computerized testing. The diagnosis of TBI was confirmed by the study physiatrist's history, physical examination, and a review of all the acute medical records, including any available battlefield information, from the time of the traumatic event to the present, using the DoD definition of TBI. The only exclusion criteria were the presence of a disorder that contraindicated hyperbaric exposure or previous exposure to HBO_2. Volunteers were recruited from a pool of full-duty Marines from Camp Lejeune Marine Base (North Carolina) and a few from Marine Base Quantico (Virginia) whose symptoms were being managed by the TBI clinic but who were otherwise without medical or military limitations. The Marines from Quantico received additional duty orders to relocate to Naval Medicine Operational Training Center at Naval Air Station Pensacola, Florida, for 2 months to receive the investigative exposures in a hyperbaric chamber.

Demographic information, clinical parameters, and baseline physical, cognitive, and behavioral functioning measures were obtained. Participants were randomly assigned to breathe 1 of 3 oxygen mediums in the hyperbaric chamber at 2.0 ATA, specifically 10.5%, 75%, or 100% oxygen. The sham control (10.5% oxygen at 2.0 ATA) simulated a placebo exposure. The intervention dosing used in this study was chosen on the basis of consensus opinion of the DoD and VA.[16] To maximize participant blinding, oxygen concentrations were varied while maintaining 2.0 ATA to minimize the likelihood of participants noting differential pressures. Randomization to 1 of the 3 groups was accomplished using a computer-generated number assignment (randomizer.org).

Exposures were conducted in a multiplace chamber, with the breathing medium delivered at gas flow rates of 20 L/min or more, using an oxygen treatment hood once the 2.0 ATA exposure pressure was reached, to ensure a consistent dose (Amron International Inc, Vista, California). The Naval Medicine Operational Training Center hyperbaric chamber was elevated less than 50 ft above mean sea level. Exposures in this study were delivered using modifications of established protocols developed by the Navy's Bureau of Medicine and Surgery (BUMED) Undersea Medicine Department. To ensure distributional uniformity among the 3 experimental exposures, subjects were accessioned in 5 separate blocks of 11 to 15 subjects, based on subject availability. Each group of subjects was randomly assigned to receive 1 of the 3 experimental conditions. Once assigned to a particular treatment group, the subjects' experimental condition did not vary over the 40-exposure course. To ensure subject and investigator blinding to the specific treatment exposure being received, all subjects were pressurized inside the chamber to a pressure equivalent of 2.0 ATA. This is equivalent to the atmospheric pressure attained during underwater diving to 33 ft of seawater. Subjects breathed an oxygen-nitrogen treatment gas blended to achieve the oxygen pressure equivalents to which they were assigned. Specifically, 3 gas mixtures were used: (1) a sham air equivalent of 10.5% oxygen (balance 89.5% nitrogen); (2) a 1.5 ATA oxygen exposure equivalent of 75% oxygen (balance 25% nitrogen); and (3) a 2.0 ATA oxygen exposure equivalent of 100% oxygen (0% nitrogen). Chamber compression to 2.0 ATA generally required less than 3 minutes to attain. Once at 2.0 ATA of pressure, each subject was instructed to sit quietly and breathed the assigned gas mixture for a period of 60 minutes (SD = ±1 minute). Chamber decompression to 1.0 ATA (ie, an average room air pressure of 759 mm Hg) similarly required less than 3 minutes to attain. Each participant underwent 40 compressions lasting 60 minutes over a 10-week period. During compression to and decompression from 2.0 ATA, all subjects breathed ambient chamber air. Taking into account the National Fire Protection Agency, US Navy Diving Manual Class A chamber operation standards and local Naval Medicine Operational Training Center control levels, the oxygen content of chamber air was closely regulated to remain between 19% and 23.5% surface equivalents (ie, sea level). This protocol was selected because it most closely approximated the community standard of care and met all safety guidelines.[7,8]

Any subject unable to complete a scheduled treatment due to transient contraindications to hyperbaric chamber exposure (ie, fevers, congestion, inability to equalize sinus or ear pressure) was allowed to make up the missed treatment at the next available opportunity (ie, later the same day, on weekends when treatments were not normally scheduled, or, if necessary, during the transition period between the five 12-subject blocks).

Statistical analyses

This segment of the study focused on an analysis of the effects of these exposures on the primary outcome measure, the Rivermead Postconcussion Symptom Questionnaire (RPQ), by comparing baseline measures with initial postcompression outcomes. Subsequent analyses of all outcome measures at both the initial and 3-month time periods will be completed later. Initial postcompression outcome measurements were obtained within the first week following last exposure. While a broad array of outcome batteries was used for all participants, this initial article presents main findings on the symptomatic effects of the chamber exposures measured by the primary outcome tool, the RPQ.[17] The RPQ is a widely used Likert-type symptom inventory consisting of 16 items (and a 17th narrative item) designed to evaluate the somatic, cognitive, and emotional functioning of individuals who have PPCS following a brain injury.[17] A study of the psychometric properties of the RPQ found that it is most appropriately scored and analyzed using 2 subscales, items 1 to 3 constituting the RPQ-3 and the remaining 13 items constituting the RPQ-13.[17] The appropriate sample size estimates were calculated for a 10% difference (equal to a decrease of 7 total score points) on the primary outcome of postconcussion symptom severity as measured by the RPQ,[17] which required 20 subjects in each group after adjusting for 10% attrition (1-way analysis of variance [ANOVA]; power = 0.80; α = .05). Given the significant co-occurrence of PTSD in military populations with mTBI[1–4] and the overlap of many symptoms to either condition, several behavior measures were included in this investigation. For this article, we selected the Posttraumatic Disorder Checklist–Military Version (PCL-M) to assess symptoms associated with PTSD.[16,18] The PCL-M is a 17-item self-report measure of symptoms suggestive of PTSD and is often used

as an aid in screening for and measuring PTSD. For both the RPQ and the PCL-M, improvement in symptoms is denoted by lower scores.

All analyses were conducted using SPSS 16.0. Demographic characteristics were analyzed using descriptive statistics. Main effect concussive symptom changes were examined using 1-way ANOVA of scores pre- and postcompression on RPQ individual items, RPQ subscales (RPQ-3; RPQ-13), and RPQ total score. Potential secondary effects of hyperbaric treatment on posttraumatic stress was analyzed using 1-way ANOVA on PCL individual item scores pre- and postcompression as well as PLC total score. Statistical level of significance was set at .05.

RESULTS

One hundred twenty eight SMs met preliminary study eligibility and consented for evaluation. Sixty-one of 128 candidates met the full-study criteria and were randomly assigned into the sham control or 1 of 2 HBO_2 exposure groups. The primary reasons for exclusion were the inability to confirm the diagnosis of mTBI, active medication changes, and schedule conflicts. One participant was unavailable for the immediate postintervention assessment, leaving a total of 60 subjects for this analysis. All study subjects experienced at least 1 mTBI, with the most recent TBI occurring at a mean of 8.5 months (SD = 6.58 months; range = 3-39 months) prior to the baseline assessments. All subjects were men. Etiology of concussion included improvised explosive device blast (85.3%), rocket-propelled grenades (3.0%), and mortar attacks (1.7%). The remaining 10% were uncategorized blasts. Slightly more than a quarter of the participants self-reported concussions ($M = 2.1$, SD = 0.95; range = 1-4) prior to the most recent blast injury. Of the 60 subjects who completed the pre- and postcompression procedures, there were 21 subjects in the sham compression group, 18 in the 1.5 ATA equivalent group, and 21 in the 2.0 ATA equivalent group. There were no precompression between-group differences on these variables.

The final sample of 60 subjects had a mean age of 23.2 years (SD = 2.95). Two subjects (3.0%) were African American, 47 (78.3%) were white, 10 (16.6%) were Hispanic, and 1 (1.6%) was Native American. Of the 60 subjects, 19 were married, 3 were divorced, and 38 were single. Pay grades E1 to E6 comprised 97% of the sample. One-way ANOVA and χ^2 analysis revealed no between-group differences with respect to age, pay grade, marital status, or race /ethnicity.

To determine whether a main effect existed, between-group analyses, using SPSS with 1-way ANOVA, were conducted for the pre- and postcompression RPQ items, subscales (RPQ-3; RPQ-13), and total scores. As a secondary analysis, PCL-M item responses and total score, again using SPSS with 1-way ANOVA, were also conducted. At pretreatment, there were no significant differences between groups for symptom inventory items, verifying the efficacy of randomization. At postcompression, no significant differences were found between the 3 groups on any individual symptom inventory items, subscale scores (RPQ-3; RPQ-13), or total scores on the RPQ or PCL-M (see Tables 1 and 2).

Within-group analyses were conducted for all 3 groups, using paired t tests, comparing pre- and postcompression RPQ item responses. The sham (2.0 ATA-10.5% O_2) group showed no significant differences on symptom inventory items, subscale scores (RPQ-3; RPQ-13), or total score. The 1.5 ATA equivalent (2.0 ATA-75% O_2) group showed a statistically significant increase (ie, worsening) on item 14 (light sensitivity), but no significant differences were noted for other symptom individual items, subscale scores (RPQ-3; RPQ-13), or total score. The 2.0 ATA equivalent (2.0 ATA-100% O_2) group showed a statistically significant decrease on items 4 (noise sensitivity) and 9 (frustration, impatience), but no other significant differences were noted for symptom individual items, subscale scores (RPQ-3; RPQ-13), or total score (see Table 3).

Within-group analyses were then conducted for all 3 groups, using paired t tests, comparing pre- and postcompression PCL-M item responses. Items 16 (being super alert; watchful) and 17 (easily startled) were significantly decreased within the sham (2.0 ATA-10.5% O_2) group, but no other significant differences were noted for individual symptom inventory items or total score. The 1.5 ATA equivalent (2.0 ATA-75% O_2) group showed a significant decrease on item 16 (being super alert; watchful), but no other significant differences were noted for individual symptom inventory items or total score. The 2.0 ATA equivalent (2.0 ATA-100% O_2) group demonstrated significant decreases on PCL-M items 4 (upset when reminded of stressful past event) and 16 (being super alert; watchful) and total score (see Table 4).

DISCUSSION

This investigation represents the second DoD-VA collaborative, randomized, controlled clinical trial studying clinically relevant effects of HBO_2 on PPCS. In this study, none of the groups achieved the hypothesized clinically significant improvement (ie, 7 points) on the primary outcome measure for PPCS (ie, RPQ). In addition, there were no significant differences between groups on any of the RPQ-3, RPQ-13, or PCL-M total scores postcompression. While there were within-group improvements on several of the items for each of the 3 compression groups, analysis of individual symptom items revealed that there were no between-group

TABLE 1 *Between-group analysis of RPQ item means*

	Precompression				Postcompression			
Item no.	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***
1	2.9	3	2.83	.83	2.62	2.90	2.39	.35
2	1.57	1.43	1.22	.63	1.76	1.52	1.28	.27
3	0.76	0.62	0.55	.78	0.71	0.76	0.33	.24
4	2.7	2.10	2.72	.28	2.43	2.48	2.00	.32
5	2.52	2.86	2.83	.63	2.86	2.86	2.61	.75
6	2.24	1.7	1.72	.28	2.24	1.76	1.78	.31
7	2.62	2.38	3.05	.16	2.48	2.62	2.50	.92
8	1.38	1.0	1.17	.60	1.24	1.10	0.94	.77
9	2.52	2.43	2.67	.78	2.33	2.19	2.11	.79
10	3.14	3.05	3.06	.94	3.05	3.0	2.78	.67
11	2.43	2.19	2.44	.75	2.52	2.29	2.39	.75
12	2.57	2.29	2.39	.69	2.33	2.38	2.06	.58
13	1.29	0.71	0.67	.15	1.48	1.0	0.67	.06
14	1.62	1.10	0.94	.18	1.90	1.62	1.11	.16
15	0.48	0.43	0.28	.58	0.81	0.33	0.22	.07
16	2.05	2.05	1.94	.96	2.10	1.76	1.50	.36
RPQ-3	5.20	5.04	4.6	.72	5.10	5.19	4.00	.20
RPQ-13	27.57	24.29	25.83	.48	27.76	25.38	22.67	.23
Total score	32.81	29.33	30.44	.53	32.86	30.57	26.67	.19

Abbreviations: ATA, atmospheres absolute; RPQ, Rivermead Postconcussion Symptom Questionnaire.

differences. These findings are similar to the first DoD-VA collaborative trial.[9] The lack of between-group differences among the 3 experimental conditions on the primary outcome measure suggests that there was no treatment effect that could be attributed to the HBO_2 parameters studied. These current findings, which parallel the earlier work of Wolf and colleagues,[9] are particularly important in that this study used the more typical treatment pressures advocated by hyperbaric clinicians.[8,10,12,13]

TABLE 2 *Between-group analysis of PCL-M item means*

	Precompression				Postcompression			
Item no.	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***
1	2.95	2.81	3.39	.24	2.71	2.67	2.83	.90
2	2.43	2.86	3.16	.11	2.38	2.76	3.00	.25
3	2.10	1.76	2.39	.15	1.90	1.95	2.00	.96
4	2.52	2.52	2.94	.46	2.48	2.48	2.28	.80
5	2.71	2.57	2.72	.93	2.76	2.52	2.52	.56
6	2.57	2.57	2.72	.92	2.52	2.57	2.39	.89
7	2.0	2.05	2.22	.82	1.90	2.14	1.83	.62
8	2.0	2.38	2.28	.63	2.24	2.43	2.17	.82
9	2.19	2.10	2.61	.49	2.19	1.71	2.17	.31
10	2.29	2.33	3.00	.15	2.42	2.29	2.50	.87
11	2.57	2.33	2.89	.47	2.48	2.19	2.33	.80
12	1.71	1.57	1.61	.91	1.71	1.81	1.28	.23
13	3.71	3.86	3.83	.93	3.95	3.76	3.50	.53
14	3.38	3.38	3.55	.87	3.14	3.05	3.14	.91
15	3.33	3.10	3.44	.58	3.43	3.24	3.33	.86
16	3.24	3.29	3.11	.88	2.76	2.86	2.39	.52
17	3.43	3.19	3.43	.69	2.90	2.86	3.00	.94
Total score	45.14	44.67	49.39	.45	43.9	43.29	42.56	.96

Abbreviations: ATA, atmospheres absolute; PCL-M, Posttraumatic Disorder Checklist–Military Version.

TABLE 3 *Within-group analysis of RPQ item means*[a]

	Sham			1.5 ATA equivalent			2.0 ATA equivalent		
Item no.	Precompression mean	Postcompression mean	*P*	Precompression mean	Postcompression mean	*P*	Postcompression mean	Precompression mean	*P*
1	2.9	2.62	.23	3.00	2.90	.71	2.83	2.39	.12
2	1.57	1.76	.33	1.43	1.53	.73	1.22	1.28	.83
3	0.76	0.71	.83	0.62	0.76	.48	0.55	0.33	.33
4	2.7	2.43	.21	2.10	2.48	.23	2.72	2.00	.04[b]
5	2.52	2.86	.18	2.86	2.86	1.0	2.83	2.61	.33
6	2.24	2.24	1.0	1.71	1.76	.88	1.72	1.77	.88
7	2.62	2.48	.51	2.38	2.62	.26	3.06	2.50	.10
8	1.38	1.24	.42	1.00	1.10	.72	1.17	0.94	.22
9	2.52	2.33	.38	2.43	2.19	.37	2.67	2.11	.05[b]
10	3.14	3.05	.65	3.05	3.00	.72	3.06	2.78	.45
11	2.43	2.52	.68	2.19	2.29	.68	2.44	2.39	.88
12	2.57	2.33	.40	2.29	2.38	.75	2.38	2.06	.33
13	1.29	1.48	.30	0.71	1.00	.21	0.67	0.67	1.0
14	1.62	1.90	.28	1.10	1.62	.04[b]	0.94	1.11	.64
15	0.48	0.81	.11	0.43	0.33	.49	0.22	0.22	1.0
16	2.05	2.10	.87	2.05	1.76	.44	1.94	1.50	.15
RPQ-3	5.20	5.10	.84	5.04	5.19	.8	4.6	4.0	.32
RPQ-13	27.57	27.76	.91	24.29	25.38	.59	25.83	22.67	.21
Total score	32.81	32.86	.98	29.33	30.57	.61	30.44	26.67	.19

Abbreviations: ATA, atmospheres absolute; RPQ, Rivermead Postconcussion Symptom Questionnaire.
[a]Significant items were #4 (noise sensitivity), #9 (frustration, impatience), and #14 (light sensitivity).
[b]Significant.

TABLE 4 *Within-group analysis of PCL-M item means*[a]

	Sham			1.5 ATA equivalent			2.0 ATA equivalent		
Item no.	Precompression mean	Postcompression mean	*P*	Precompression mean	Postcompression mean	*P*	Precompression mean	Postcompression mean	*P*
1	2.95	2.71	.37	2.81	2.67	.63	3.39	2.83	.14
2	2.43	2.38	.86	2.86	2.76	.68	3.16	3.00	.51
3	2.10	1.90	.46	1.76	1.95	.43	2.39	2.00	.13
4	2.52	2.48	.88	2.52	2.48	.85	2.94	2.28	.02[b]
5	2.71	2.76	.88	2.57	2.52	.83	2.72	2.52	.30
6	2.57	2.52	.88	2.57	2.57	1.0	2.72	2.39	.21
7	2.0	1.90	.68	2.05	2.14	.75	2.22	1.83	.15
8	2.0	2.24	.46	2.38	2.43	.89	2.28	2.17	.54
9	2.19	2.19	1.0	2.10	1.71	.23	2.61	2.17	.16
10	2.29	2.42	.64	2.33	2.29	.87	3.00	2.50	.07
11	2.57	2.48	.72	2.33	2.19	.65	2.89	2.33	.22
12	1.71	1.71	1.0	1.57	1.81	.17	1.61	1.28	.11
13	3.71	3.95	.33	3.86	3.76	.80	3.83	3.50	.32
14	3.38	3.14	.31	3.38	3.05	.23	3.55	3.14	.32
15	3.33	3.43	.74	3.10	3.24	.58	3.44	3.33	.71
16	3.24	2.76	.03[b]	3.29	2.86	.05[b]	3.11	2.39	.04[b]
17	3.43	2.90	.03[b]	3.19	2.86	.15	3.43	3.00	.19
Total score	45.14	43.9	.67	44.67	43.29	.64	49.39	42.56	.05[b]

Abbreviations: ATA, atmospheres absolute; PCL-M, Posttraumatic Disorder Checklist–Military Version.
[a]Significant items were #4 (upset when reminded of past stressful event), #9 (being super alert; watchful), and #17 (easily startled).
[b]Significant.

While no main treatment effect was found at any exposure level, within-group analyses were noteworthy for improvements on 1 to 2 items from both the RPQ and the PCL-M within each experimental condition. In addition, the total score for the 2.0 ATA equivalent group for the PCL-M was found to improve. A statistical argument could be made that the total score is subject to family-wise error rate, and a post hoc test (eg, Bonferonni correction or a similar test) should have been conducted to reduce the likelihood of false-positives by lowering the α value. It was determined, given the exploratory nature of this feasibility study, that doing so would have increased the number of false-negatives, obscuring statistically significant results. Future studies should apply the more rigorous post hoc corrections to ensure that false-positives are not included (ie, type I error). However, it is interesting to note that even with a more "liberal" α value, these significant results represented only a small fraction of the item inventory and a restricted symptom array. The 6 symptoms that significantly varied within any of the groups were noise sensitivity, light sensitivity, easily frustrated, easily upset by past events, being super alert, and easily startled. Three of these symptoms (being super alert, easily upset, and easily startled) are hallmarks of PTSD but are not typical for mTBI. One of them (easily frustrated) may be seen in either condition, and the remaining 2 symptoms (noise and light sensitivity) are more commonly associated with mTBI. The finding of symptoms consistent with mTBI or PTSD or both was expected in this cohort because of the nature of postdeployment syndrome.[1–6] While one of the symptoms (noise sensitivity) that improved within the 2.0 ATA equivalent exposure group is most commonly associated with mTBI, none of the symptoms improved differentially in the main analysis between groups.

The decision to use the RPQ as the primary outcome measure was driven by its worldwide acceptance in the study of mTBI and specifically PPCS.[15,19,20] However, it is most commonly used for individuals who are within 1 year of their symptom-generating mTBI, when these symptoms are most likely to improve or resolve. In this investigation, while the mean time post-mTBI was 8.5 months, many of the subjects had multiple mTBIs, some as distant as 39 months previously, and symptom onset could not be easily discerned. Moreover, these subjects had most likely already experienced the bulk of the recovery typically seen following mTBI, but persistent residual symptoms remained at the time of study enrollment. However, the baseline mean individual item score on the RPQ for all groups was 1.93; therefore, these subjects could only have improved in a limited fashion as compared with individuals with the more typical moderate-severe symptoms seen with acute concussion. The preestablished clinically significant RPQ total score criterion threshold of a 7-point improvement was not approached in any of the groups. Of interest, we found that the sham and 1.5 ATA equivalent groups demonstrated nonsignificant increase (worsening) in their raw total RPQ scores, whereas the 2.0 ATA equivalent group demonstrated a 3.77-point nonsignificant decrease (improvement).

We believe that the improvements seen in this investigation, as well as in the study of Wolf and colleagues and prior case reports,[11,12,21–23] can be best explained by factors other than the effect of HBO_2 on PPCS. As has been reported in depression, anxiety, and PTSD randomized sham-controlled trials, one would expect a placebo and/or Hawthorne effect on symptoms, given the intense nature of the intervention.[24–26] For example, the Marines in this study were temporarily reassigned to Naval Air Station Pensacola and had greatly reduced duty schedules. In addition, they had enhanced access to leisure time and activities in a noncombat, semitropical beach environment. The significant improvement on the PCL-M total score in the 2.0 ATA equivalent group is of interest, but its implications are unclear. Given evidence from animal research on the positive effects of HBO_2 on behavioral factors[27] and the minor benefits seen on the PCL-M in the 2.4 ATA DoD trial,[9] further prospective investigations may be warranted.

This trial represents the second randomized, double-blinded, sham-controlled, prospective study of HBO_2 in the population of subjects with symptomatic chronic mTBI and demonstrates no significant symptomatic improvements from PPCS of HBO_2 at either 1.5 or 2.0 ATA equivalent over sham control. This investigation incorporated many features lacking in prior studies, such as randomization, blinding, and control groups. The inclusion of this level of scientific rigor in this study and the study of Wolf and colleagues support the conclusion that the minor benefits seen on the RPQ, the PCL-M, and other similar measures are not the result of HBO_2.

These studies demonstrated that individuals with PPCS could be recruited into and safely tolerate this study protocol. Future studies, which are currently underway, will benefit from the addition of a waiting list or standard concussion care third arm to account for the nonspecific effects possible in sham control treatment and longer duration of follow-up to assess for the durability of any initial improvements.

This study has several inherent limitations. The small sample size limits the power of the study. Generalizability may be limited by gender. In addition, the high follow-up rate seen secondary to the paid travel and active-duty status (ie, they received additional duty orders to be on the base) may be atypical of nonmilitary populations. The combat exposure experienced by all study participants introduces the possible influence of posttraumatic stress, depression, anxiety, substance abuse, and pain, which have been associated

with deployment,[3,4] likely had confounding effects on HBO_2. The diagnosis of TBI relies on participant self-report, which is sensitive to subjective patient interpretation, memory, social desirability, and other covariates such as personality factors and willingness to reveal problems. As noted, a confounding role of PTSD symptoms may be especially important, as our study demonstrated a significant reduction in some individual items on both the RPQ and the PCL-M that are commonly attributed to stress in both the sham control group and the HBO_2 group over time. Better understanding of this influence and other possible variables, such as time postinjury, medication usage and adjustments, and the role of repetitive mTBI in postconcussion recovery, would allow for a greater refinement of treatment protocols.

CONCLUSIONS

HBO_2 therapy is a proven intervention for treating select acute and chronic ischemic injuries that have well-established theoretical underpinnings and a well-documented role in dive-related injuries, soft-tissue healing, and carbon monoxide poisoning treatment. Prior human research trials with acute, severe TBI have been inconclusive, and previous studies among participants with long-standing postconcussion syndrome have demonstrated no symptom relief with HBO_2. This study, which used a randomized, controlled, double-blinded design conducted at total oxygen doses most commonly used by clinicians, did not demonstrate significant effects of HBO_2 in individuals with symptoms of chronic mTBI when compared with sham compression.

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