Hyperbaric Oxygen for SMs with PCS after mTBI:

A Randomized, Double-Blinded, Sham-Controlled, Variable Dose Prospective Trial

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Poll Question #1

- What is your primary role in VA?
  - student, trainee, or fellow
  - clinician
  - researcher
  - manager or policy-maker
  - Other

Use of HBO_2 : Animal Research

- Systemic review of animal (rodent, cat, dog) research <u>supports</u> HBO_2 use in acute TBI
- Acutely, HBO_2 significantly
  - Reduces <u>acute</u> cerebral edema
  - Reduces markers of cerebral <u>inflammation</u>
  - Increases cerebral perfusion
  - Enhances spatial learning / task
- Also shown to enhance cognitive outcomes in chronic moderate-severe TBI

Use of HBO_2 : Animal Research

- Caveats in examining animal literature:
  - HBO_2 treatment initiation
    - Animals usually begun minutes to 2 hours post injury
    - Humans usually 6+ hours to days post-injury
  - No HBO_2 research in mTBI (acute or chronic)
  - mTBI animal model lacking and PCS hard to understand in animal
  - No direct translation of animal TBI work to humans

Use of HBO_2 : Human Research

- Four Systematic Reviews
  - Included 23 publications (1972-2001)
  - Only four studies (382 subjects, 199 HBO_2 & 183 controls) met review criteria for scientific evaluation
  - Assessed acute, traumatic, moderate-severe TBI
  - Concluded current scientific evidence insufficient to prove effectiveness / ineffectiveness of HBO_2 for TBI

- Two reviews and two trials published since 2001.

Use of HBO_2 : Human Research

- Summary of acute human usage (in severe TBI):
  - One trial showed trend ($P \leq 0.08$) towards favorable outcome at 1.5 years post-injury.
  - Three trials showed a significant reduction (RR 0.69, 95%CI 0.54-0.88) in risk of dying (mortality) with 'numbers needed to treat' being 7.
  - No reduction in coma persistence or duration.
  - Enhanced mortality seems to be related to effects on ICP and pulmonary status

Use of HBO_2 : Human Research

- Caveats of Human Literature:
  - Overall study quality assessed as low
  - No sham therapy included
  - Randomization inadequate
  - Blinding not used
  - Non-standard inclusion criteria across trials
- No scientifically rigorous human research has been published in acute mild/moderate TBI or chronic TBI of any severity.

Current Clinical Trials in the DoD and VA

- There are presently 4 DoD supported HBOT trials for persistent symptoms after mTBI.
  - Pilot study (HBOT vs Sham) completed : No effect
  - Pilot study (outcome measure validation) completed
  - Pilot study (HBOT [2 dose] vs Sham) underway – completed
  - Definitive trial begun January 2012
- There is also 1 non-DoD open-label trial (Harch – LSU) underway.
  - Non-randomized
  - No sham or control

Richmond-Pensacola HBO_2 Study

Design:

- Three arm, single-center, double blinded, dose-ranging study with sham control
- Randomly assigned to one of three conditions
- 10.5 % at 2 ATA to mimic Sham Air; 75% O_2 at 2ATA to mimic 1.5ATA at 100% $O_{2;}$ versus100% O2 at 2.0 ATA
- 40 exposures of 60 minutes each on separate days over 8-10 weeks
- Block randomization to minimize differential effects over time

Population:

- 60 active duty Marines
- mTBI in last three years (M-8.5 mos, range 3-39 mos)
- Mean age= 23.2 (SD=2.95)
- 97% of group was E1-E6

Outcome Measures

Primary:

- Rivermead Postconcussive Questionnaire (RPQ)
  - 16 Likert-type scale items

Secondary:

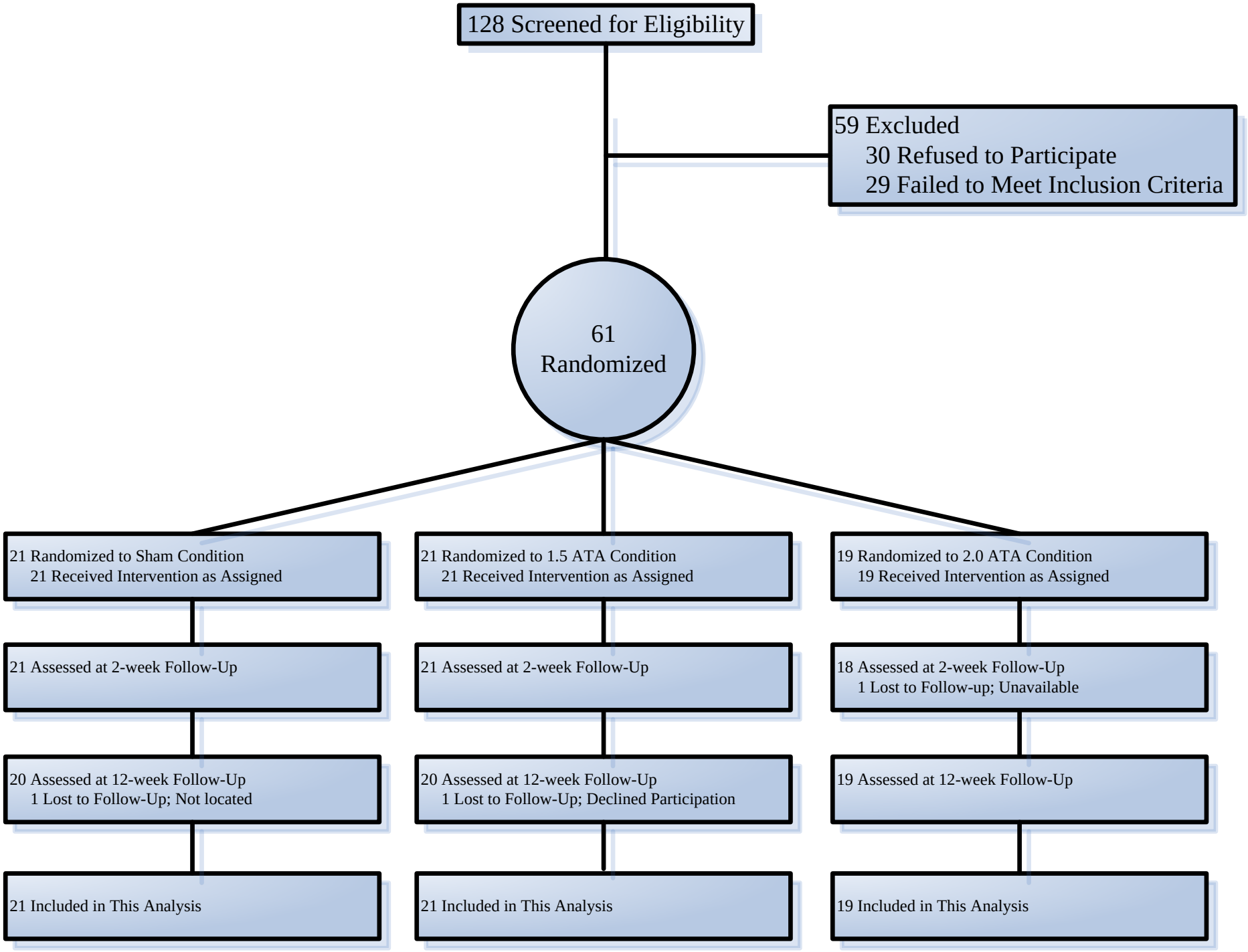
- PTSD Checklist Military (PCL-M)
  - 17 Likert-type scale items
- Both instruments are self-report measures
- Lower score indicates improvement

Tertiary:

- CPT balance, eye tracking, neuropsychological testing

Sample Selection

- Recruited primarily at MCB Camp Lejeune
- Inclusion Criteria
  - Sustained mTBI in past 3 months to 3 yrs
  - Post-Concussion Syndrome (PCS) present
  - Stable psychiatric & psychotropic medication status
- Exclusion Criteria
  - Moderate or severe TBI
  - Prior exposure to HBO2 (hyperbaric oxygen)
  - Contraindications to HBO2 (such as pulmonary “air trapping condition)


128 Screened for Eligibility
59 Excluded
30 Refused to Participate
29 Failed to Meet Inclusion Criteria
61
Randomized
21 Randomized to Sham Condition
21 Received Intervention as Assigned
21 Randomized to 1.5 ATA Condition
21 Received Intervention as Assigned
19 Randomized to 2.0 ATA Condition
19 Received Intervention as Assigned
21 Assessed at 2-week Follow-Up
21 Assessed at 2-week Follow-Up
18 Assessed at 2-week Follow-Up
1 Lost to Follow-up; Unavailable
20 Assessed at 12-week Follow-Up
1 Lost to Follow-Up; Not located
20 Assessed at 12-week Follow-Up
1 Lost to Follow-Up; Declined Participation
19 Assessed at 12-week Follow-Up
21 Included in This Analysis
21 Included in This Analysis
19 Included in This Analysis

Sample (n=61) characteristics

- Demographics
  - Age mean 23.3 years (SD=3.24).
  - 20 (33%) married, 3 (5%) divorced, and 38 (62%) single.
  - All were Marines and 97% had E1-E6 pay grades.
  - ANOVA and chi square analysis: no between group differences

- All had >= one mTBI during deployment from blast
  - 85% from improvised explosive device (IED)
  - 3.0% from rocket propelled grenade,
  - 1.7% from mortar attack
  - 10% not categorizable.
  - At “pre” assessment s participants were mean 8.5 months (SD= 6.6, range= 3-39) after most recent (or only) mTBI

Results

- There were ***no differences between any of the groups*** on any aspect of the **primary** outcome measure (RPQ), including subscales RPQ-3 and RPQ-13
- - within group comparisons (pre/post) were not significant
- No ***differences between any of the groups*** on the total score of the secondary measure (PCL-M)
  - Within group differences (pre/post):
    - Sham: 6.7 point improvement
    - HBO_2 1.5 ATA: 6.2 point improvement
    - HBO_2 2.0 ATA: 13.9 point improvement (statistically improved)

One-way ANOVA conducted on total RPQ score, subscales RPQ-3 and RPQ-13, and all individual items
One-way ANOVA conducted on total PCL-M score

Results

RPQ Sub-analysis: Within group differences on individual symptoms

- Sham group showed no significant differences between pre-post compression scores
- 1.5 ATA equivalent group showed a significant increase (worsening) in light sensitivity
- 2.0 ATA equivalent group showed a significant decrease (improvement) on noise sensitivity and frustration/ impatience

Results

<u>PCL-M Sub-analysis:</u> Within group differences on individual symptoms

- Sham group showed significant improvement on super alertness/watchfulness and being easily startled between pre-post compression scores
- 1.5 ATA equivalent group showed a significant improvement on super alertness/watchfulness
- 2.0 ATA equivalent group showed a significant improvement on being upset when reminded of a stressful event, super alertness/watchfulness and total score

Results

- Secondary Outcomes: There were ***no differences between any of the groups*** on any aspect of the **secondary** outcome measures, including subscales neuropsychological tests, balance testing and eye tracking.

- There were interactions between changes in the RPQ and the descriptive and secondary outcome measures, however this was ***not*** influenced by the intervention group they were in.

Statistical Methods

- Repeated measures mixed-effect model was used to determine efficacy of outcomes
- Primary hypothesis: RPQ-16 scores differ between intervention groups (Sham, 1.5 ATA, 2.0 ATA) across time points (0 wks, 1 wks, 12 wks)
- Model included all of the explanatory variables as well as time (0 wks, 1 wks, 12 wks), intervention group (Sham, 1.5 ATA, 2.0 ATA), and the interaction between time and intervention group.
- Evidence of intervention efficacy was determined if the parameters corresponding to the interaction term were non-zero at the 0.05 level
- This model is adjusted for following subjects longitudinally, through an unstructured covariance structure and a random effect accounting for the cohort

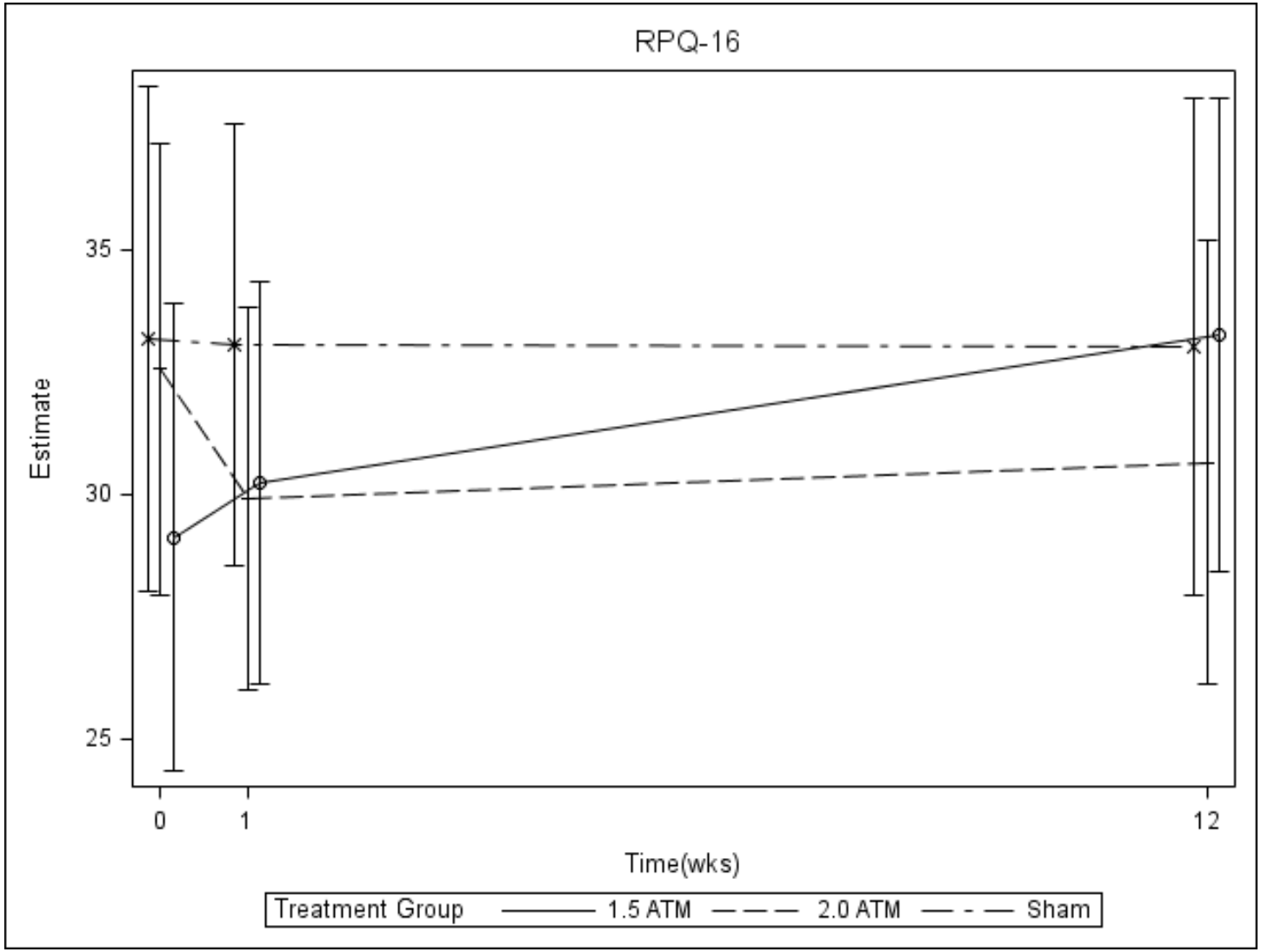
Explanatory variable distribution by intervention group

Variable	Level	Sham	1.5 ATA	2.0 ATA	*P*
Blast Exposure	High (≥ 4)	8 (38%)	8 (38%)	6 (32%)	0.887
	Low (< 4)	13 (62%)	13 (62%)	13 (68%)	
LOC	Yes	8 (38%)	12 (57%)	6 (32%)	0.231
	No	13 (62%)	9 (43%)	13 (68%)	
PTA	Yes	13 (62%)	15 (71%)	8 (42%)	0.161
	No	8 (38%)	6 (29%)	11 (58%)	
PTSD	Yes (PCL ≥ 50)	6 (29%)	6 (29%)	10 (53%)	0.359
	No (PCL < 50)	15 (71%)	15 (71%)	9 (47%)	
TOMM	Pass	19 (90%)	18 (86%)	14 (74%)	0.340
	Fail	2 (10%)	3 (14%)	5 (26%)	
Time Elapsed	≤ 6 mos	11 (52%)	9 (43%)	11 (58%)	0.627
	> 6mos	10 (48%)	12 (57%)	8 (42%)	
Drinking Status	High Risk	11 (52%)	11 (52%)	11 (58%)	0.923
	Low Risk	10 (36%)	10 (48%)	8 (42%)	
Previous Head Injury	Yes	3 (15%)	6 (32%)	7 (33%)	0.349
	No	17 (85%)	13 (68%)	14 (67%)	
Age		24 (1.2) [b]	22.9 (2.9) [b]	22.9 (3.3) [b]	0.326[a]
WTAR (baseline)		33.9 (6.1) [b]	32.9 (6.5) [b]	34.0 (6.0) [b]	0.828[a]
McGill Score (baseline)		11.9 (8.3) [b]	12.0 (6.0) [b]	10.4 (8.8) [b]	0.780[a]

Explanatory variable main effects on RPQ-16.

Explanatory Variable	F-ratio(df1, df2)	*P*-value
Time	0.9 (2, 55.5)	0.426
Intervention Group	0.5 (2, 47.2)	0.590
Blast Exposure	2.6 (1, 48.2)	0.112
PTA	**4.8 (1, 48.4)**	**0.033**
LOC	0.9 (1, 48.1)	0.350
PTSD	**7.3 (1, 48.5)**	**0.009**
Injury Elapse	2.4 (1, 48.3)	0.131
Alcohol Use	1.5 (1, 129)	0.219
Age	0.0 (1, 50.1)	0.925
Previous Head Injury	0.0 (1, 48.1)	0.937
McGill	**33.4 (1,143)**	**<0.001**
WTART	1.2 (1,119)	0.278
TOMM	0.1 (1, 47.7)	0.730

RPQ-16 by intervention group over time (baseline, 1 wk, 3 month)



Time by intervention group effect = (F(4, 63.7)=1.0, *P*=0.410)

Hypothesis tests for secondary outcomes (treatment by time interaction)

Predictor	F-ratio (df1, df2)	*P*
RPQ-3	0.7 (4, 64.0)	0.592
RPQ-13	1.0 (4, 63.8)	0.400
Mayo	0.6 (4, 62.8)	0.702
Balance (SOT)	1.0 (4, 58.9)	0.443
WAIS	1.8 (4, 59.4)	0.141
Trail-Making B	0.7 (4, 64.9)	0.621
Stroop	0.6 (4, 60.2)	0.664
CPT-II	0.6 (4, 60.9)	0.685
CVLT Long Delay Free Recall	0.8 (4, 63.1)	0.523
PASAT	1.4 (4, 52.9)	0.256
BVMT Delay Recall	0.5 (4, 62.3)	0.753
COWAT	1.6 (4, 64.1)	0.197
Grooved Peg Board	0.5 (4, 47.5)	0.724
SWLS	0.5 (4, 61.2)	0.751
Depression (CESD)	0.5 (4, 63.8)	0.767
GOSE	0.8 (4, 57.7)	0.503

Hypothesis tests for subgroup efficacy analysis (RPQ-16)

[3 way interaction between explanatory variable, time, and treatment group]

Explanatory Variable	F-ratio(df1, df2)	*P*
Blast Exposure	0.57 (4, 62.8)	0.685
PTA	1.00 (4, 62.9)	0.416
LOC	0.20 (4, 63.4)	0.938
PTSD	0.13 (4, 63.9)	0.971
Injury Elapse	0.67 (4, 63.1)	0.618
Alcohol Use	0.27 (4, 65.4)	0.898
Age	0.78 (4, 69.3)	0.539
Previous Head Injury	2.06 (4, 62.1)	0.097
McGill	0.12 (4, 72.6)	0.975
WTAR	0.67 (4, 69.1)	0.618
TOMM	0.83 (4, 66.5)	0.510

Results

- RPQ was influenced by a number of secondary factors, however was not influenced by intervention group.
  - RPQ decreased over time
  - RPQ was higher when there was a marker of more significant mTBI (# of blast-related mTBI, presence or absence of PTA)
  - RPQ was higher when there was an increased report of body pain.
  - RPQ was higher when there was evidence of PTSD

Results

- There were interactions between changes in the RPQ and the descriptive and secondary outcome measures, however this was ***not*** influenced by the intervention group they were in.

- In the full analyses of secondary outcomes there was significant main effects for:
  - Time on multiple neuropsychological tests (WAIS III working memory, Trails B, CVLT LD Free Recall, PASAT 2.0 sec, BVMT Del Recall, COWAT Let Fluency). These tests improved over time but were not influenced by group.
  - LOC for SOT (computerized posturography). Worsened if subject had more mTBI or longer PTA but not influenced by group.
  - # Blast Exposures for Trails B. Worsened if subject had more mTBI or longer PTA but not influenced by group.

Conclusions

- Study duplicated total oxygen doses most often used clinically, and recommended by advocates

- No main-effect treatment differences in post-concussion symptoms were found ***between*** sham compression, 1.5 ATA or 2.0 ATA groups

- In addition to the expected significant association between PCS and PTSD symptom measures there was also an association between PCS and Pain (McGill) and mTBI with PTA versus without PTA status

TITLE: The Effect of Hyperbaric Oxygen on Persistent Post-Concussive Symptoms

RUNNING TITLE: The Effect of Hyperbaric Oxygen on Persistent Post-Concussive Symptoms

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Funding was provided for the primary study by a Defense Advanced Research Projects Agency grant (N66001-09-2-206), U.S. Navy Bureau of Medicine and Surgery for contract funding temporary duty requirements, and the U.S. Army Medical Materiel Development Activity for end of study contract funding. Dr. Carne's and 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.

Disclaimer: The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs, Department of Defense, or the U.S. Government.

Abstract

The effects of hyperbaric oxygen (HBO_2) on persistent post-concussion symptoms in 60 military service members with at least one 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 (NMOTC) at Naval Air Station Pensacola. 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 one of 3 pre-assigned 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 Postconcussive Symptom Questionnaire (RPQ) and individual and total Post-Traumatic Disorder Check List-Military Version (PCL-M) were measured just prior to intervention and immediately post-intervention. Between groups testing of pre- and post-intervention means revealed no significant differences on individual or total scores on the PCL-M or RPQ, demonstrating a successful randomization and no significant main effect for HBO_2 at 1.5 ATA or 2.0 ATA equivalent compared with the sham compression. Within group testing of pre- and post-intervention means revealed significant differences on three individual items and 2.0 ATA HBO_2 PCL-M total score. This study demonstrated that HBO_2 at either 1.5 or 2.0 ATA equivalent had no effect on post-concussive symptoms after mild TBI when compared with a sham compression.

Key words: hyperbaric oxygen therapy, traumatic brain injury, post-concussive syndrome

INTRODUCTION

With the onset of the Afghanistan and Iraq Wars in October 2001, the U.S. 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 (OEF; Afghanistan War) and Operation Iraqi Freedom (OIF; Iraq War) Veterans enrolled in the VA system of care through 2011 reveal that 9.6% experienced at least one mTBI during their deployments.[2] Of note, more than 90% of these individuals have at least one concomitant secondary diagnosis (e.g., post-traumatic stress disorder (PTSD), pain) that may confound both the clinical presentation and subsequent treatment.[2,3] This condition has been labeled Post-Deployment Multi-Symptom Disorder,[4] or more commonly Post-Deployment Syndrome[5] and may be one of the reasons for the higher rate of persistent post-concussive syndrome (PPCS) in military personnel compared to civilian individuals.[3] The broad range and high frequency of various symptoms is the clinical hallmark of these syndromes. Additionally, 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 treatments for the array of symptoms seen with PPCS in U.S. combatants, the DoD and VA have developed an initiative involving three 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.

HBO_2 administration 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 mmHg 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 in treating TBI is based on the still unproven theory that functionally retrievable neurons, adjacent to severely damaged or dead neurons, exposed to hyperbaric oxygen 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, immune modulation, 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 traumatic brain injury (i.e., more than three months post event), and the only published randomized clinical trial investigating HBO_2 for post-concussion syndrome demonstrated no effect.[9]

A typical HBO_2 clinical treatment uses oxygen at 2.0 to 3.0 ATA for durations 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 VA-DoD 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 three-arm, randomized, blinded, sham-controlled trial.

MATERIALS AND METHODS

Commencing in 2009, the Defense Advanced Research Projects Agency and U.S. Navy Bureau of Medicine and Surgery (as part of the DoD-VA collaborative research program) sponsored this single center, three-arm, randomized, blinded, sham-controlled trial of HBO_2 exposure on symptomatic mTBI. 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 United States military bases. Inclusion criteria were TBI specialist-confirmed diagnosis of mTBI based on the DoD definition of TBI (Health Affairs 2007), post-concussive 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 one 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 (NC) and a few from Marine Base Quantico (VA) 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 (NMOTC) at Naval Air Station Pensacola, Florida for two 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 one of three 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 based on the consensus opinion of the DoD and VA.[15] To maximize participant blinding, oxygen concentrations were varied while maintaining 2.0 ATA in order to minimize the likelihood of participants noting differential pressures. Randomization to one of the three 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 $\geq$20 l/min using an oxygen treatment hood once the 2.0 ATA exposure pressure was reached, to ensure a consistent dose (Amron International Inc., Vista, CA). The NMOTC hyperbaric chamber was elevated less than 50 feet 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. In order to ensure distributional uniformity among the three experimental exposures, subjects were accessioned in five separate blocks of 11-15 subjects, based on subject availability. Each group of subjects was randomly assigned to receive one of the three 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 feet of seawater. Subjects breathed an oxygen-nitrogen treatment gas blended to achieve the oxygen

pressure equivalents to which they were assigned. Specifically, three gas mixtures were employed: 1) a sham air equivalent of 10.5% oxygen (balance 89.5% nitrogen), 2) a 1.5 ATA oxygen equivalent of 75% oxygen (balance 25% nitrogen) and 3) a 2.0 ATA oxygen equivalent of 100% oxygen (0% nitrogen). Chamber compression to 2.0 ATA generally required <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 (+/- 1 minute). Chamber decompression to 1.0 ATA (i.e., an average room air pressure of 759 mmHg) similarly required <3 minutes to attain. Each participant underwent 40 compressions lasting 60 minutes over a ten-week period. During compression to and decompression from 2.0 ATA, all subjects breathed ambient chamber air. Taking into account National Fire Protection Agency, US Navy Diving Manual Class A chamber operation standards and local NMOTC control levels, the oxygen content of chamber air was closely regulated to remain between 19-23.5% surface equivalents (i.e., sea level). This protocol was selected as it most closely approximated the community standard of care and meets all safety guidelines[7,8] .

Any subject unable to complete a scheduled treatment due to transient contraindications to hyperbaric chamber exposure (i.e. fevers, congestion, inability to equalize sinus or ear pressure), was allowed to make up the missed treatment at the next available opportunity (i.e. 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 RPQ, by comparing baseline measures to initial post-compression outcomes. Subsequent analyses of all outcome measures at both the initial and 3-month time

periods will be completed later. Initial post-compression outcome measurements were obtained within the first week following last exposure. While a broad array of outcome batteries was utilized for all participants, this initial paper presents main findings on the symptomatic effects of the chamber exposures measured by the primary outcome tool, the RPQ.[16] 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.[16] A study of the psychometric properties of the RPQ found it is most appropriately scored and analyzed using two sub-scales, items 1-3 constituting the RPQ-3 and the remaining 13 items constituting the RPQ-13.[16] 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 postconcussive symptom severity as measured by the Rivermead Postconcussive Symptom Questionnaire (RPQ),[16]which required 20 subjects in each group after adjusting for 10% attrition (one way ANOVA; Power 0.80; alpha 0.05). Given the significant co-occurrence of PTSD in military populations with mTBI[1-4] and the overlap of many symptoms to either condition, a number of behavior measures were included in this investigation. For this paper, we selected the Post-Traumatic Disorder Check List-Military Version (PCL-M) to assess symptoms associated with PTSD.[15,17] The PCL-M is a 17-item self-report measure of symptoms suggestive of post-traumatic stress disorder (PTSD) and is often used as an aid in screening for and measuring PTSD. For both the RPQ and 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 one-way ANOVA of pre and post scores on RPQ individual items, RPQ subscales (RPQ-3;

RPQ-13) and RPQ total score. Potential secondary effects of hyperbaric treatment on post-traumatic stress was analyzed using one-way ANOVA on pre and post PCL individual item scoresas well as PLC total score. Statistical level of significance was set at .05.

RESULTS

One hundred and 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 one of two 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 post-intervention assessment leaving a total of 60 subjects for the present analysis. All study subjects experienced at least one mTBI, with the most recent TBI occurring a mean of 8.5 months (SD= 6.58 months, range= 3-39 months) prior to the baseline assessments. All subjects were male. Etiology of concussion included improvised explosive device (IED) blast (85.3%), rocket propelled grenades (3.0%), and mortar attacks (1.7%). The remaining 10% were uncategorized blasts. Slightly more than one-quarter of the participants self-reported concussions (M = 2.1, SD=.95, range=1-4) prior to the most recent blast injury. Of the 60 subjects who completed the pre- and post-compression 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 pre-compression between group differences on these variables.

The final sample of 60 subjects had a mean age of 23.2 years (SD=2.95). Two (3.0%) were African-American, 47 (78.3%) were Caucasian, 10 (16.6%) were Hispanic, and one (1.6%) was Native American. Of the 60, 19 were married, three were divorced, and 38 were single. Pay

grades E1-E6 comprised 97% of the sample. One-way analysis of variance (ANOVA) and chi square analysis revealed no between group differences with respect to age, pay grade, marital status, or race /ethnicity.

To determine if a main effect existed, between group analyses, using SPSS with one-way ANOVA, were conducted for the pre-compression and post-compression 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 one-way ANOVA, were also conducted. At pre-treatment there were no significant differences between groups for symptom inventory items, verifying the efficacy of randomization. At post-compression, no significant differences were found between the three groups on any individual symptom inventory items, subscale scores (RPQ-3; RPQ-13) or total scores on the RPQ or PCL-M.

*****Insert Tables 1 and 2 here****

Within group analyses were conducted for all three groups using paired t-tests, comparing pre-compression and post-compression 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 (i.e., 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, or subscale scores (RPQ-3; RPQ-13) or total score.

*****Insert Table 3 here****

Within group analyses were then conducted for all three groups using paired t-tests, comparing pre-compression and post-compression 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), 16 (being super alert; watchful) and total score.

*****Insert Table 4 here****

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 (i.e., 7 points) on the primary outcome measure for PPCS (i.e., RPQ). Additionally, there were no significant differences between groups on any of the RPQ-3, RPQ-13 or PCL-M total scores post-

compression. While there were within group improvements on several of the items for each of the three compression groups, analysis of individual symptom items revealed that there were no between group differences. These findings are similar to the first DoD-VA collaborative trial.[9] The lack of between group differences among the three experimental conditions on the primary outcome measure suggests that there was no treatment effect that could be attributed to the hyperbaric oxygen parameters studied. These current findings, which parallel the earlier work of Wolf and colleagues,[9] are particularly important in that this study utilized the more typical treatment pressures advocated by hyperbaric clinicians.[8,10,12,13]

While no main treatment effect was found at any exposure level, within group analyses were noteworthy for improvements on 1-2 items from both the RPQ and the PCL-M within each experimental condition. Additionally, 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 (e.g., Bonferonni correction or a similar test) should have been conducted to reduce the likelihood of false positives by lowering the alpha 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 in order to ensure that false positives are not included (i.e., type I error). However, it is interesting to note that even with a more “liberal” alpha value these significant results represented only a small fraction of the item inventory and a restricted symptom array. The six 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 two symptoms (noise and light sensitivity) are more commonly associated with mTBI. The finding of symptoms consistent with either (or both) mTBI and PTSD was expected in this cohort due to the nature of post-deployment 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.[15,18-19] However, it is most commonly utilized in individuals who are within one 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 mTBI's, 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 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 to individuals with the more typical moderate-severe symptoms seen with acute concussion. The pre-established 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 non-significant increase (worsening) in their raw total RPQ scores, whereas the 2.0 ATA equivalent group demonstrated a 3.77 point non-significant decrease (improvement).

We believe that the improvements seen in this investigation, as well as the Wolf study and prior case reports[11,12,20-22] can be best explained by factors other than the HBO_2's effect 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.[23-25] For example, the Marines in this study were temporarily reassigned to Pensacola Naval Air Station and had greatly reduced duty schedules. Additionally, they had enhanced access to leisure time and activities in a non-combat, semi-tropical 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[26] 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 symptomatic chronic mTBI population 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, to include randomization, blinding, and control groups. The inclusion of this level of scientific rigor in this study and Wolf's support the conclusion that the minor benefit seen on the RPQ, PCL-M and other similar measures are not the result of the hyperbaric oxygen.

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 a number of inherent limitations. The small sample size limits the power of the study. Generalizability may be limited by gender. Additionally, the high follow-up rate

seen secondary to the paid travel and active duty status (i.e., they received additional duty orders to be on the base) may be atypical of non-military populations. The combat exposure experienced by all study participants introduces the possible influence of post-traumatic 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 of some individual items on both the RPQ and PCL-M that are commonly attributed to stress in both the sham-control and HBO_2 groups over time. Better understanding of this influence and other possible variables, time post-injury, medication usage and adjustments and the role of repetitive mTBI in post-concussion recovery, would allow for a greater refinement of treatment protocols.

CONCLUSIONS

Hyperbaric oxygen treatment is a proven intervention for 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 in participants with long-standing post-concussive syndrome have demonstrated no symptom relief with hyperbaric oxygen. This study, which utilized a randomized, controlled, double-blinded design conducted at total oxygen doses most commonly by used by clinicians, did not

demonstrate significant effects of hyperbaric oxygen in individuals with symptoms of chronic mTBI, when compared to sham compression.

ACKNOWLEDGMENTS

The authors would like to 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 (U.S. Army Medical Material Development Activity (USAMMDA), Ft. Detrick, MD) for manuscript review.

Table 1
Between Group Analysis of RPQ Item Means

	Pre-Compression				Post-Compression			
Item number	Sham	1.5 ATA Equivalent	2.0 ATA Equivalent	Significance	Sham	1.5 ATA Equivalent	2.0 ATA Equivalent	Significance
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

Table 2

Between Group Analysis of PCL-M Item Means

	Pre-Compression				Post-Compression			
Item number	Sham	1.5 ATA Equivalent	2.0 ATA Equivalent	Significance	Sham	1.5 ATA Equivalent	2.0 ATA	Significance Equivalent
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

Table 3

Within Group Analysis of RPQ Item Means

	Sham				1.5 ATA Equivalent				2.0 ATA Equivalent		
Item Number	Pre Mean	Post Mean	Sig		Pre Mean	Post Mean	Sig		Pre Mean	Post Mean	Sig
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*
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*
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*		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

*Significant

n.b.: Significant items were #4 (noise sensitivity), #9 (frustration, impatience) and #14 (light sensitivity)

Table 4

Within Group Analysis of PCL-M Item Means

	Sham				1.5 ATA Equivalent				2.0 ATA Equivalent		
Item Number	Pre Mean	Post Mean	Sig		Pre Mean	Post Mean	Sig		Pre Mean	Post Mean	Sig
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*
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*		3.29	2.86	.05*		3.11	2.39	.04*
17	3.43	2.90	.03*		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*

*Significant

n.b.: Significant items were #4 (upset when reminded of past stressful event), #9 (being super alert; watchful) and #17 (easily startled)

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