Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial

E. George Wolf [1], Laura M. Baugh [2], Christine M. Schubert Kabban [3], Michael F. Richards [1], Jennifer Prye [1]

[1] U.S. Air Force School of Aerospace Medicine, 59th Medical Wing Hyperbaric Medicine Department, Lackland AFB, Texas U.S.

[2] Department of Neurology, 10th Medical Group, U.S. Air Force Academy, Colorado U.S.

[3] Department of Mathematics and Statistics/ENC Air Force Institute of Technology, Wright- Patterson AFB, Ohio U.S.

CORRESPONDING AUTHOR: Dr. E. George Wolf – *earl.wolf.ctr@us.af.mil*

ABSTRACT

Objective: Determine changes in cognition and post-traumatic stress disorder (PTSD) symptoms in subjects with traumatic brain injury (TBI) exposed to 2.4 atmospheres absolute (atm abs) breathing 100% oxygen vs. sham (1.3 atm-abs air).

Methods: Fifty randomized subjects completed a total of 30 exposures. A concussion history was taken, then baseline, post-series, and six-week follow-up immediate post-concussion assessment and cognitive testing, Brain-checkers and PTSD Checklist for Military (PCL-M) tests were administered.

Results: No statistically significant differences between groups were noted, but both groups improved. Subgroups analyses, based on concussion history and individual test components, showed improvement in the treatment group vs. the sham. These subgroups included the number of concussive events, time from event to consent, loss of consciousness, visual memory, processing, go – no go, and simple reaction time.

Conclusion: There was no statistically significant difference between a sham and 2.4 atm abs hyperbaric oxygen (HBO_2) in cognitive scores from ImPACT and Brain-checkers or composite scores in the PCL-M; however both groups showed improvement. Subgroups with favorable response to treatment are identified. Future studies evaluating HBO_2 should consider concussion histories or focus on validating subgroup response to determine HBO_2 as a potential adjunctive treatment for persistent symptoms following TBI.

INTRODUCTION

Traumatic brain injury (TBI) from the blast and impact effects of explosive devices is the signature wound of recent military conflicts. As of May 2015, there have been 327,299 TBIs diagnosed from January 2000-March 2015 [1]. Of these, 269,580 were diagnosed with mild TBI. Some of these individuals with mild TBI have persistent symptoms for more than three months following the concussive events. These symptoms include cognitive, physical and emotional complaints, many of which overlap with symptoms of post-traumatic stress disorder (PTSD). Treatment focuses on primary care provider- based symptom relief and education (mental, physical and social well-being), with referral to mental health care for behavioral symptoms, cognitive therapy and TBI specialists if the symptoms persist [2]. Comple-mentary and alternative medicine (CAM) and integrative medicine approaches for TBI and PTSD have gained acceptance, but research is still needed to validate efficacy [3]. More recent efforts include mindfulness approaches [4], psycho-educational computer-based treatment [5], biofeedback, Tai Chi, yoga and others [6].

Hyperbaric oxygen (HBO_2) is an adjunctive treatment for indications such as delayed radiation injury, central retinal artery occlusion, sudden sensorineural

KEYWORDS: traumatic brain injury, hyperbaric oxygen, cognitive function, TBI, HBO, HBO_2, HBOT, hydrostatic pressure, PTSD, post-traumatic stress disorder, PCL, PCL-M, PCL-C

hearing loss, intracranial abscess, compromised grafts and seven other formal indications [7]. HBO_2 works by using standard gas laws to dissolve oxygen into the liquid part of the blood that is then delivered throughout the body with enough oxygen dissolved to bypass hemoglobin. This is the basis for HBO_2 use in treating carbon monoxide poisoning and resultant acute cerebral injury and delayed neuropsychiatric syndrome [8].

In 2008, we developed the protocol to look at the potential use of HBO_2 as an adjunctive treatment of TBI based on the future research recommendations from an Agency for Healthcare Research and Quality (AHRQ) review [9]. One of the AHRQ recommendations was to look at the safety of using HBO_2 in the TBI population. A randomized clinical trial was conducted from 2009-2011, which demonstrated that the exposure of 2.4 atmospheres absolute (atm abs) hyperbaric oxygen was safe for TBI patients with no significant side effect differences to that of the 1.3-atm abs (air) sham [10]. The study also confirmed that a sham treatment could successfully be accomplished in a multiplace hyperbaric chamber. Comparison of baseline and post-intervention testing between the sham-control and HBO_2 group revealed no significant differences on the PTSD Checklist for Military (PCL-M) composite score or on the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) total symptoms score. Of note, PCL-M composite scores and ImPACT total symptoms scores for both sham-control and HBO_2 groups revealed improvement over the course of the study [11]. This report presents the results of cognitive testing and further analysis of the PCL-M questionnaire changes from that study.

MATERIALS AND METHODS

This study was approved by the Wilford Hall Ambulatory Surgical Center Institutional Review Board. The Air Force Medical Service, the U.S. Navy Bureau of Medicine and Surgery, the U.S. Army Medical Materiel Development Activity, the Wounded Warrior Regiment USMC, the USAF School of Aerospace Medicine and the Injured Marine Semper Fi Fund supported this study, but no organization had any role in the study design, data collection or analysis.

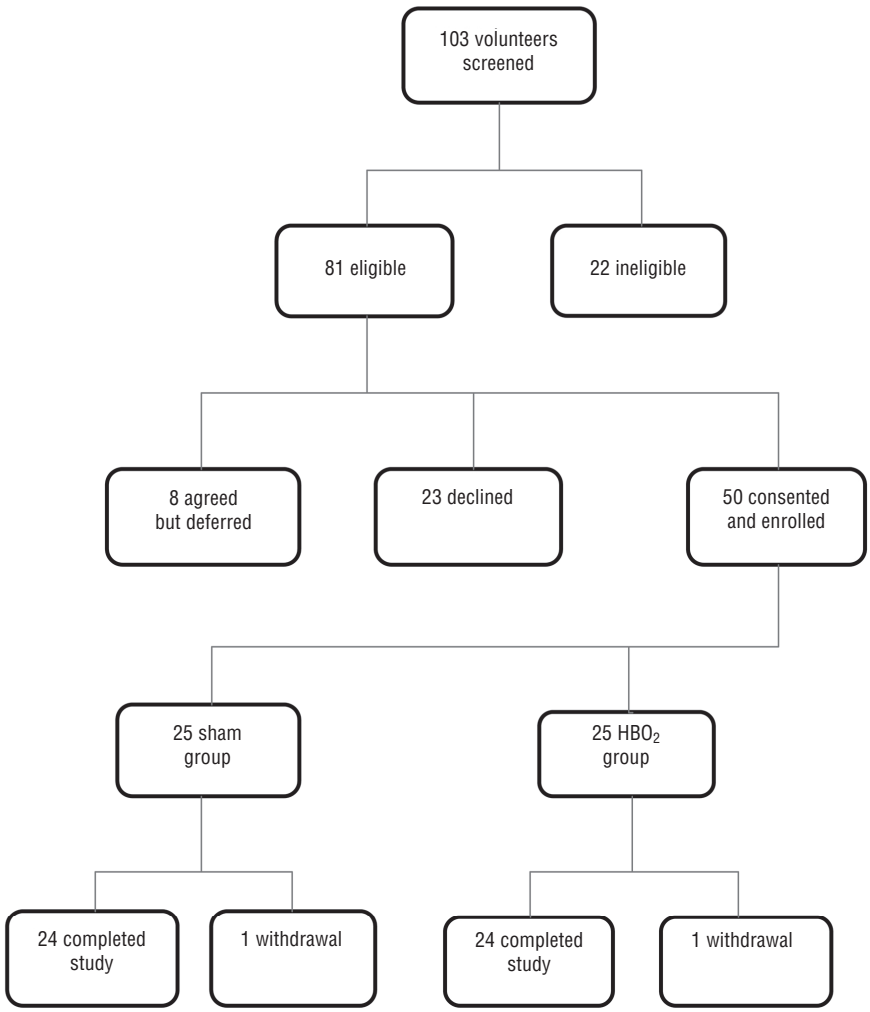
Details of the study methods and summary statistics are described in references 10 and 11 as well as in the study diagram (Figure 1). Fifty TBI subjects were randomized to 30 exposures for either the sham or HBO_2 series as identified above. The range of subject ages was from 20 to 51 years of age, with a mean of 28.32 years and a standard deviation (SD) of 7.7 years. Inclusion criteria for the subjects included:

- diagnosis of TBI after October 2001;
- perception of cognitive dysfunction following their injury;
- stable mental status for at least two months;
- stable psychotropic medication history for at least one month;
- persistence of TBI-associated symptoms;
- the ability to perform ImPACT® [12], Braincheckers (a personal digital assistant (PDA) version of the Automated Neuropsychological Assessment Metrics (ANAM)) [13] and Test of Variables of Attention.

The time period from a subject's most recent concussion to consent ranged from three to 71 months. These subjects met the definition and criteria of post-concussive syndrome (PCS), with persistent symptoms in individuals who have sustained mild traumatic brain injuries [14]. Individual composite scores from the ImPACT and Braincheckers computer programs were obtained prior to intervention, after every five exposures, and at six-week follow-up.

ImPACT is a widely used, 20-minute computerized cognition assessment that generates composite scores related to concussion sequelae. Composite scores include verbal memory, visual memory processing speed and reaction time. Maerlender reported that significant correlations were found in convergent validity studies between traditional neuropsychological measures and all of the composite scores above [15]. Echemendia demonstrated ImPACT baseline use for detecting neurocognitive deficits following sports concussion as well as using post-concussion data alone (no baseline) in identifying clinically meaningful post-concussion cognitive decline [16]. Schatz showed that ImPACT baselines remain stable for two years provided no concussion event occurs [17]. Resch [18] showed test-retest over a one-week period demonstrated an intraclass correlation coefficient (ICC) range of 0.71-0.84 (processing speed), 0.78-0.88 (reaction time), 0.41-0.59 (verbal memory) and 0.26-0.85 (visual memory). For the 45-day test-retest, comparable to the six-week

Figure 1. Study flow diagram



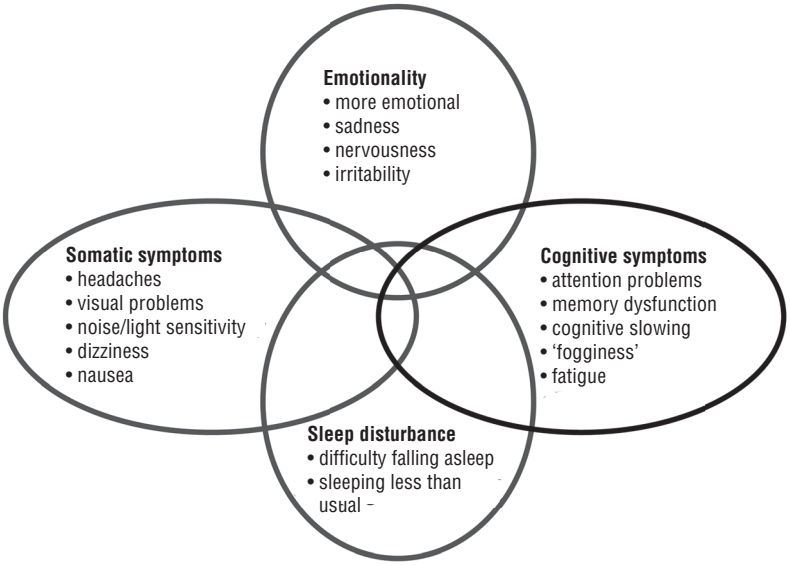
Study flow diagram – Age range: overall 20-51, mean 28.32, SD 7.7; sham 21-46, mean 28.4; SD 7.4; treatment 20-51, mean 28.3, SD 8.1. Time from last injury to consent: overall 3-71 months, mean 30.7, SD 18.4; sham 5-71, mean 34.0, SD 19.6; treatment 3-62; mean 27.4, SD 16.8. Gender: 23 males/1 female in each group

follow-up, Nakayama, [19] demonstrated the ICC was 0.87 (processing speed), 0.67 (reaction time), 0.76 verbal memory, and 0.72 (visual memory).

Braincheckers is a PDA version of ANAM, supported by the Army Medical Research and Materiel Command. It was validated against ANAM [20 – available by request from author; 21] for the individual tests used. Jones demonstrated that the ANAM had equivalent reliability to Woodcock-Johnson III Tests of Cognitive Ability and the General Intellectual Ability tests [22]. Kaminski [23] used intraclass correlation coefficients to demonstrate an excellent range of agreement in an ANAM test-retest stability study. Bryan [24] demonstrated that Service Members (SM) who were diagnosed with TBI after deployment had significant decreases in ANAM scores from predeployment scores compared to SMs who were not diagnosed with TBI post-deployment. ANAM is used as a predeployment baseline for the military [25].

The PCL-M is a 17-item self-report measure of symptoms suggestive of PTSD. The questionnaire was administered at the same frequency and the composite scores obtained. Gore [26] showed a PCL-M test-retest reliability of 0.87.

Figure 2. Post-concussion symptoms and categories



A comprehensive history and physical examination were conducted prior to and after the hyperbaric exposures series and the six-week follow-up. A concussive event was defined as one that met the DoD definition of TBI [2] and symptoms immediately following the head injury event based on those in Figure 2 [27]. The concussion interview consisted of main categories: the number of concussive events; whether the subject also had multiple exposures; if there were two concussive events within a 48-hour period; duration from the event to consent in individuals who had only a single event or the most recent event if more than a single concussive event was identified; the etiology of the event; and whether loss of consciousness (LOC) occurred (not required as part of the DoD TBI definition). The etiology of the event was either from a blast, a head impact, or both. Exposures were defined as potentially concussive events in which the individual was exposed to blast or impacts but did not experience symptoms. For this investigation, two concussive events within 48 hours were defined as "close events." These events were identified to determine whether a difference existed in the subgroup with repeated exposures in succession, potentially prior to full recovery from the first concussion.

METHODS

Repeated measures analysis of covariance (ANCOVA) and repeated measures analysis of variance (RMANOVA) were used to test for differences between groups. In addition, the various composite scores from ImPACT, Braincheckers and PCL-M were ranked using the baseline, post-exposure series, and the six-week follow-up scores. These were separated by subject number and within groups for subjects who improved and those who did not, resulting in four groups:

- sham improved;
- sham not improved;
- HBO_2 improved; and
- HBO_2 not improved.

Table 1 is an example of the process of segregating the improved/not improved subjects in the sham and control groups in regard to ImPACT processing speed. Using blast etiology as a demonstration, there were 11 subjects who improved in the sham group, seven who did not improve in the sham group, four who did not improve in the HBO_2 group and 10 subjects in the treatment group who improved. This was done for each cognitive subtest and PCL-M against each concussion history category.

Table 1. Improved vs. unimproved

category	number	mult expo	close events	ev to con	etiology	LOC
	7127	0	0	25	1	1
	7388	1	0	43	1	1
	7393	0	0	58	1	1
	7556	0	0	8	2	1
	7642	1	0	18	1	0
SHAM	7650	0	0	5	2	0
IMPROVED	7755	1	1	8	2	0
	7934	1	0	51	1	0
	7971	1	0	28	1	1
	7991	1	0	25	1	1
	7256	1	0	32	1	0
	7469	1	0	24	1	0
	7717	1	0	55	1	1
	7811	0	0	30	1	1
	7816	1	1	58	1	0
	7817	1	0	47	3	3
	7972	0	0	49	3	1
	7172	1	1	18	3	0
SHAM NOT	7491	1	0	70	1	1
IMPROVED	7628	1	0	12	1	1
	7718	1	0	18	1	0
	7812	0	0	35	1	1
	7848	1	0	29	1	0
	7941	0	0	71	1	1
WITHDREW	7490	1	0	51	1	1
	7529	0	0	9	3	0
	7416	1	1	22	1	0
	7575	1	0	26	1	1
TREATMENT	7218	1	1	22	2	0
NOT IMPROVED	7283	1	0	58	3	2
	7443	0	0	18	1	0
	7698	1	1	43	3	1
	7827	0	0	21	1	0
	7161	1	0	26	1	0
	7176	0	0	12	1	1
	7180	1	0	42	1	0
	7228	0	0	62	3	1
	7258	0	0	19	1	0
	7287	0	0	17	2	0
TREATMENT	7433	1	0	33	1	0
IMPROVED	7727	0	0	53	3	1
	7900	1	0	39	1	0
	7220	0	1	34	2	1
	7322	0	1	5	1	1
	7430	1	0	4	1	1
	7457	0	0	33	1	0
	7696	0	0	41	2	2
	7875	1	0	4	2	1
	7895	0	0	3	3	0
	7966	0	0	19	1	1

After ranking, the relative risk of improvement (RROI) was calculated. Evolving the results to percentage of those improved demonstrates the potential for more subjects to improve based on intervention. Since statistical methods such as ANOVA compare groups on averaged means that may not reflect the potential benefits occurring to a larger number of subjects experiencing treatment vs. sham, we also examined the relative improvement seen. This allowed the post-hoc application of relative risk analysis, using MedCalc [28], to identify potential subgroups for future investigation. All statistical models were run in SAS v9.2 and verified resulting relative risk values. The RROI values were aggregated to determine concussion history category and subtest improvement most likely to benefit from treatment.

Resulting ImPACT scores consisted of verbal memory, visual memory, processing speed, and response time. Braincheckers scores are based on component tests code substitution, procedural reaction time, go–no go reaction time, matching to sample, code substitution recall, and simple reaction time. Braincheckers scores are reported as reaction time and throughput. PCL-M composite score changes of 5 to 9 points improvement are considered reliable changes, and 10 or greater are considered significant changes. Relative risk calculations were separated into values of 1.0 or less, >1.0 to 1.4, and any value ≥ 1.5.

Delineation of improved and not improved subjects: example of segregated scores for ImPACT Processing.

number = subject identifier;

mult expo = asymptomatic exposures/ yes(1) no(0);

close event = 2 concussions within 48 hours/ yes (1) no (0);

ev to con = months from last concussion to study consent;

etiology = blast (1), impact (2) or both (3);

LOC = loss of consciousness/ yes (1) no (0).

RESULTS

General details of the study methods and resulting summary statistics for this sample of subjects is pictured in Figure 2 and have been previously described [10,11]. For concussion history, 36% of the subjects had a single concussive event, 34% had two events, 22% had three events, and 8% had four or more events.

ImPACT: Overall, subjects demonstrated significant cognitive problems on the ImPACT. When subjects were compared to both a military and general population matched for age, the index categories at baseline ranged from impaired to low aver-age. This confirmed that subjects with a history of TBI selected for the study had measurable cognitive deficits. ANCOVA showed no significant statistical differences between groups at any time point for visual memory, verbal memory, or reaction time. RMANOVA demonstrated improvement in each measurement over time for ImPACT visual memory and time processing ($p<0.05$), but no statistically significant difference between the groups. The percentage of subjects who improved from baseline to post-exposure series or six-week follow-up was 58% in the sham group and 67% in the HBO_2 group.

Braincheckers: Scores were not significantly different for any measurement between sham and treatment groups. Results from RMANOVA with speed and accuracy scores for code substitution recall, matching to sample, and simple reaction indicated improvement in each measurement over time for both groups ($p<0.05$), but no statistically significant difference between the groups.

PCL-M: There were no significant differences between groups at any time point for the composite score using ANCOVA. RMANOVA indicated improvement in each measurement over time for both groups for composite scores ($p<0.05$), but no statistically significant difference between the groups.

Relative Risk of Improvement: Identified cells (Tables 2-4) represent scores/concussion where the RROI of HBO_2 vs. the sham fell within the following three parameters: clear (1.0 or less); gray (> 1.0 to 1.4); and dark gray (any value ≥ 1.5). To narrow down identification of potential subgroups, those subgroups and individual tests that had >50% of the overall gray/dark-gray cells were identified by the light-gray cells in the last row and column in each chart. As the study is relatively small, this approach avoids overstating the preliminary trends in this pilot study while focusing on the subgroups with the largest effects. The PCL-M (Table 5) RROI was also computed against the concussion history in both those subjects who had reliable (may be due to intervention) and significant (likely to be due intervention) changes. The discussion focuses on those who had significant improvement by definition.

DISCUSSION

Relative risk of improvement

On cognitive testing, subjects who had three concussive events had the best RROI when in the treatment group. In subjects with a single event, Braincheckers scores had an RROI in > 50% of the individual tests. This may be of practical importance, as many military members have had more than one concussive event that was symptomatic (64% in this study). If the ImPACT threshold was lowered to 50% of the test scores, it also demonstrated an RROI for individuals with a single concussive event. The PCL-M data demonstrated a >1.0 RROI in those subjects who had two or three concussive events. These data suggest that having greater than one concussive event should not be excluded for any future TBI studies looking at hyperbaric oxygen as a potential treatment.

Many subjects had multiple blast and/or impact exposures with no concussive symptoms in addition to their concussive events. The RROI for subjects who experienced two concussive events within 48 hours (close events) was seen only across the cognitive function tests in ImPACT. Subjects with non-concussive exposures did not demonstrate a positive RROI in the cognitive test batteries. Of note however, there was a significant RROI in those subjects who had multiple asymptomatic exposures in the PCL-M. This may be in line with ongoing debates as to the etiology of PTSD symptoms comorbid with mild traumatic brain injury (mTBI): Are they related to the life-threatening situation under which the TBI occurred, or is there damage at a physiologic level that causes the PTSD symptoms? The significant decrease in PCL-M scores associated in subjects having a history of multiple asymptomatic exposures would favor the former argument. When

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Table 2. ImPACT composite scores vs concussion history

History Concussions	ImPACT Composite scores				
	Verbal mem	Visual mem	Processing	Response	STR
1					2
2					2
3					3
4					1
Multiple exp					
Yes					2
No					1
Close event					
Yes					3
No					2
Consent time					
Single event					
< 1 year					4
< 2 years					3
2-4 years					2
> 4 years					1
Most recent					
< 1 year					3
< 2 years					3
2-4 years					1
> 4 years					1
Etiology					
Blast only					2
Impact only					1
Both					1
All Blast					2
All Impact					1
LOC					
Yes					2
No					2
Total	4	14	19	8	
RROI > 1.0 to 1.49	RROI ≥ 1.5	≥ 50% row or column			

Relative Risk of Improvement:

Identified cells (Tables 2-4) represent scores/concussion where the RROI of HBO$_2$ vs. the sham fell within three parameters:

clear (1.0 or less);

gray (> 1.0 to 1.4); and dark gray (any value ≥ 1.5).

Subgroups and individual tests that had >50% of the overall gray/dark-gray cells were identified by the light-gray cells in the last row and column in each chart.

RROI = relative risk of improvement; Verbal mem = verbal memory; Visual mem = visual memory; Processing = processing speed; Response = response time; STR: subtotal of cells with RROI > 1.0 in rows; Multiple exp = asymptomatic blast or impact exposures; Consent time = time from last recorded concussion segregated by individuals with only a single concussion or the most recent concussion in subjects with more than one concussion; LOC = loss of consciousness. Total = number of cells with RROI > 1.0 in columns. ≥ 50% row or column = 50% or more of number of data cells in a row or column have RROI > 1.0,

Table 3. Braincheckers speed scores vs. concussion history

	Braincheckers reaction time (speed)						
History Concussions	**CDS**	**PRO**	**GNG**	**MSP**	**CDD**	**SRT**	**SCR**
1							4
2							0
3							4
4							0
Multiple exp							
Yes							1
No							3
Close event							
Yes							3
No							0
Consent time							
Single event							
< 1 year							4
< 2 years							5
2-4 years							1
> 4 years							1
Most recent							
< 1 year							4
< 2 years							1
2-4 years							2
> 4 years							3
Etiology							
Blast only							1
Impact only							1
Both							6
All Blast							2
All Impact							3
LOC							
Yes							4
No							0
Total	8	12	8	3	9	13	
RROI > 1.0 to 1.49	RROI ≥ 1.5		≥50% row or column				

Relative Risk of Improvement:

Identified cells (Tables 2-4) represent scores/concussion where the RROI of HBO$_2$ vs. the sham fell within three parameters:

clear (1.0 or less);

gray (> 1.0 to 1.4); and

dark gray (any value ≥ 1.5).

Subgroups and individual tests that had >50% of the overall gray/dark-gray cells were identified by the light-gray cells in the last row and column in each chart.

CDS = code substitution learning; PRO = procedural reaction time; GNG = go-no go; MSP = match to sample; CDD = code substitution, delayed recall; SRT = simple reaction time; SCR = subtotal of cells with RROI > 1.0 in rows; Multiple exp = asymptomatic blast or impact exposures; Consent time = time from last recorded concussion segregated by individuals with only a single concussion or the most recent concussion in subjects with more than one concussion; LOC = loss of consciousness. Total = number of cells with RROI > 1.0 in columns. ≥ 50% row or column = 50% or more of number of data cells in a row or column have RROI > 1.0.

Table 4. Braincheckers accuracy scores vs. concussion history

	Braincheckers throughput (accuracy)							
Concussions	**CDS**	**PRO**	**GNG**	**MSP**	**CDD**	**SRT**	**STR**	**TOT**
1							3	7
2							2	2
3							4	8
4							0	
Multiple exp								
Yes							2	3
No							1	4
Close event								
Yes							2	5
No							1	1
Consent time								
Single event								
< 1 year							5	9
< 2 years							2	7
2-4 years							2	2
> 4 years							1	2
Most recent								
< 1 year							5	9
< 2 years							1	2
2-4 years							2	4
> 4 years							5	8
Etiology								
Blast only							1	2
Impact only							1	2
Both							5	11
All Blast							2	4
All Impact							1	4
LOC								
Yes							4	8
No							1	1
Total	6	6	15	3	7	16		
RROI > 1.0 to 1.49	RROI ≥ 1.5		≥ 50% row or column					

Relative Risk of Improvement:

Identified cells (Tables 2-4) represent scores/concussion where the RROI of HBO$_2$ vs. the sham fell within three parameters:

clear (1.0 or less);

gray (> 1.0 to 1.4); and dark gray (any value ≥ 1.5).

Subgroups and individual tests that had >50% of the overall gray/dark-gray cells were identified by the light-gray cells in the last row and column in each chart.

CDS = code substitution learning; PRO = procedural reaction time; GNG = go-no go; MSP = match to sample; CDD = code substitution, delayed recall; SRT = simple reaction time; STR = subtotal of cells with RROI > 1.0 in rows; Tot = total of STR columns from Tables 2 and 3; Total RROI > 1.0 in columns. Multiple exp = asymptomatic blast or impact exposures; Consent time = time from last recorded concussion segregated by individuals with only a single concussion or the most recent concussion in subjects with more than one concussion; LOC = loss of consciousness; ≥ 50% row or column = 50% or more of number of data cells in a row or column have RROI > 1.0

Table 5. PCL-M composite scores vs concussion history

	Composite scores		
Concussions	**Reliable chng**	**Signif chng**	
1			
2			1
3			2
4			
Multiple exp			
Yes			2
No			
Close event			
Yes			1
No			
Consent time			
Single event			
< 1 year			
< 2 years			
2-4 years			
> 4 years			
Most recent			
< 1 year			2
< 2 years			2
2-4 years			
> 4 years			
Etiology			
Blast only			
Impact only			2
Both			
All blast			
All impact			1
LOC			
Yes			1
No			
Total	8	6	
RROI > 1.0 to 1.49	RROI ≥ 1.5	≥ 50% row or column	

Relative Risk of Improvement:

Identified cells (Tables 2-4) represent scores/concussion where the RROI of HBO$_2$ vs. the sham fell within three parameters:

clear (1.0 or less);

gray (> 1.0 to 1.4); and dark

gray (any value ≥ 1.5).

Subgroups and individual tests that had >50% of the overall gray/dark-gray cells were identified by the light-gray cells in the last row and column in each chart.

Reliable chng = reliable change (5-9 points); Signif chng = significant change (10 or more points); Multiple exp = asymptomatic blast or impact exposures; Consent time = time from last recorded concussion segregated by individuals with only a single concussion or the most recent concussion in subjects with more than one concussion; LOC = loss of consciousness; ≥ 50% row or column = 50% or more of number of data cells in a row or column have RROI > 1.0.

isolating subjects who had a diagnosis of PTSD by PCL-M definition (score >50) the hyperbaric oxygen at 2.4 atm abs group had a 77% significant improvement of 10 or more points, when compared to 33% in the sham chamber sessions. This is further described by Scorza [29], who used these study data to determine if hyperbaric oxygen is efficacious for the treatment of comorbid PTSD with mild TBI.

In subjects with a single event, it appears the RROI is best if HBO_2 can be started within two years of injury in regard to the cognitive test batteries. Even more so, on cognitive testing an RROI $\geq$ 1.5 was predominant in subjects who were within one year of injury. The RROI in the PCL-M data did not reflect this observation for subjects with only a single event. The RROI in the ImPACT scores reflected the same two-year pattern in individuals who sustained more than one concussion. In the Braincheckers data, subjects who sustained more than one concussion appeared to respond better to hyperbaric oxygen therapy if started within one year. PCL-M in subjects with multiple concussive events had an RROI if HBO_2 was started within two years and showed the same deference to starting within one year of the event.

Etiology was broken down into subjects who experienced blast, impact, or both in each of their respective concussive events. This allowed a breakout of those who had only a blast or impact etiology. The RROI was best in Braincheckers in subjects whose concussion involved both impact and blast components. When using 50% as a threshold in the ImPACT scores, cognitive function improved in subjects who had a blast etiology. Significant changes in PCL-M RROI were seen in subjects who had an impact etiology. These RROIs would infer that improvement in cognitive function is associated more with a blast etiology whereas PTSD improvement was associated more in subjects who had an impact etiology.

LOC was an important concussion history component in Braincheckers scores. LOC did not seem to be a discriminator in the history for either ImPACT or the PCL-M scores. Concussion history was only one aspect of identifying subgroups that potentially showed benefit of hyperbaric oxygen therapy. The other means was observing significant RROI in the individual test composite scores in each of the cognitive test batteries.

ImPACT derives composite scores from six test modules: word discrimination, design memory, X's and O's, symbol matching, color match, and three-letter memory [30]. Within individual test composite scores (identified in Methods and Materials), visual memory and processing speed in ImPACT had a majority of positive RROI cells across the concussion history categories. Braincheckers tests were also identified in Methods and Materials, and scores are reported as reaction time and throughput. These have been translated into speed and accuracy, respectively, for this discussion. Speed scores had a majority of positive RROI cells in procedural reaction time and simple reaction time. Accuracy scores had a majority of positive RROI cells for go-no go and simple reaction time across the concussion history categories. The go-no go test represents critical cognitive functions for infantry in accurately determining an enemy vs. friendly and whether to fire their weapon; simple reaction time is critical in making that decision quickly.

These are important test subgroups since both ImPACT and ANAM are used clinically. ImPACT is used extensively in the athletic community, with baseline testing preseason in concussion-prone sports, and used post-concussion as a means of determining return to play for the athlete. ANAM is routinely administered to military personnel prior to deployment and may be repeated upon return from deployment as a means of tracking cognitive function or later following a head injury.

These relationships set up a strategy in tailoring the use of HBO_2 as a treatment depending on the individual's concussion history or screening cognitive tests that show low scores compared to the individual's baseline tests. For example, an individual with a single concussive event 18 months ago, whose post-event scores are low on processing speed and simple reaction time, may be a prime candidate for hyperbaric oxygen exposures vs. an individual with a single concussive event five years ago, whose post-event scores are low only on verbal memory and match-to-sample subtests.

Oxygen and pressure

One factor to consider is that the sham could be considered an oxygen treatment in that the partial pressure of oxygen is increased (as well as that of nitrogen).

Table 6. Oxygen doses of various air or oxygen protocols

pressure (abs)	partial O_2 (mmHg)	time (min)	O_2 dose (mHg*min)	days	cumulative O_2 dose (mHg*min)
1 atm air	159.6	60	9.6		
1 atm air	159.6	90	14.4		
1 atm 100% O_2	760	90	68.4	40	2736
1.2 atm air	191.52	60	11.5	40	460
1.2 atm air	191.52	90	17.2	40	688
1.3 atm air	207.48	60	12.5	30	375
1.3 atm air	207.48	90	18.7	30	561
1.3 atm .24% O_2	237.12	90	21.3	40	852
1.5 atm 100% O_2	1140	60	68.4	40	2736
1.5 atm 100% O_2	1140	90	102.6		
1.7 atm 100% O_2	1292	90	116.3		
2.0 atm 10.5% O_2	159.6	60	9.6	40	384
2.0 atm 75% O_2	1140	60	68.4	40	2736
2.0 atm 100% O_2	1520	60	91.2	40	3648
2.0 atm 100% O_2	1520	90	136.8	30	4104
2.4 atm 100% O_2	1796.34	90	161.7	30	4851
3.0 atm 100% O_2	2280	90	205.2		

Another factor is the increased hydrostatic pressure created with both the sham and the treatment arms. This could, in part, explain why both groups had improvement in the cognitive tests and the PCL-M. The partial pressure of oxygen and overall dose will be considered first, followed by the hydrostatic pressure.

This study used hyperbaric oxygen at 2.4 atm abs in the treatment leg and 1.3 atm abs air, dropping to 1.2 atm abs after 10 minutes for the remainder of the hyperbaric exposure. In order to accurately compare the various "treatment" profiles, a dose relation table was developed (Table 6). This included the partial pressure of oxygen delivered at 1.0, 1.2, 1.3, 1.5, 1.7, 2.0, 2.4, and 3.0 atm abs. These pressures were used as they were common in clinical hyperbaric medicine (2.0, 2.4 and 3.0), in the published studies (or proposed – 1.7 atm abs) or in anecdotal reports (1.5 atm abs). These were then calculated for time and number of exposures to obtain a cumulative oxygen dose represented as meters of mercury minutes or mHg*min (Wolf). This is the same concept used in radiation oncology, where a total dose is spread over a number of individual sessions. For the study, this resulted in a total oxygen dose of 4,851 mHg*min for the treatment leg compared to 561 mHg*min for the sham. The treatment exposure delivered 8.65 times the oxygen dose compared to the sham. The anecdotal dose at 1.5 atm abs yields, at most, a cumulative dose of 2736 mHg*min for the typical 40 one-hour exposures (this assumes 100% from beginning to end that will not be possible using a monoplace chamber). The study treatment dose is 1.77 times the anecdotal dose. The anecdotal dose is 4.88 times the sham dose used in this study. An interesting finding was that the anecdotal dose of oxygen is equivalent to breathing 100% oxygen at 1.0 atm abs for 90 minutes per day for 40 days. If these last two profiles are oxygen-equivalent, yet 1.5 atm abs anecdotal exposures claim positive findings, then does the hydrostatic pressure itself have an effect?

Pressure effect has been considered since the early 20th century [31], but it has been more actively studied since the 1990s, predominantly in cell culture experiments. Dean, et al. [32] mention hydrostatic pressures ranging from 1.17 to 4.0 atm abs can alter neuronal excitability in dorsal root ganglion neurons. In his study graphs, the neuron firing rate demonstrated a gradual increase and an increase in membrane conductance in a neuron in the solitary complex of the caudal-dorsal medulla oblongata as hydrostatic pressure increased from 1 atm abs to 3 atm abs. Dean speculates that neuronal barosensitivity to relatively low levels of hyperbaric pressure may be the early stage of a pressure continuum that is eventually exhibited as high-pressure nervous syndrome at higher pressures seen in the diving community.

A follow-up study by Mulkey, et al. [33] suggests neuronal barosensitivity occurs possibly as low as 100 mmHg (1.13 atm abs or 0.13 atm gauge). Macdonald and Fraser (34) have proposed that many non-neuronal cells respond to micropressures, which they define as 20 kPa (0.2 atm gauge or 1.2 atm

abs), by a mechanical process that they hypothesize to be localized shear and strain forces resulting from the differential compression of various adjoining cellular components, such as lipid bilayers, membrane-bound proteins, cytoskeletal proteins, and extracellular matrix.

Gao, Feng, and Liao [35] incubated vascular smooth muscle and endothelial cells in various hydrostatic pressures. The most obvious proliferation of vascular smooth muscle cell was detected under the pressure of 16 kPa (1.16 atm abs), with greatest cell activity, and the most obvious proliferation of vascular endothelial cell, was under 20 kPa (1.2 atm abs) pressure.

The effect of hyperbaric pressure in gene expression regulation is also an active research area. Chen, et al.'s [36] microarray analysis of gene expression after exposure of rat neurons to varying levels of partial oxygen pressures showed that more genes were altered in response to hyperbaric air (2-, 4-, and 6 atm abs) than hyperbaric oxygen. Godman, et al. [37] demonstrated that a single 2.4 atm abs oxygen exposure activated the expression of cytoprotective and growth-promoting genes in endothelial cells and was dependent on elevated pressure used in standard hyperbaric oxygen treatments.

Kendall, et al. [38] exposed endothelial cells to a chronic wound model composed of 2% oxygen at 1 atm abs for 24 hours. Cells then underwent 90 minutes of hyperbaric oxygen at 1.5 atm abs and 2.4 atm abs (2.0 atm abs not studied) to simulate treatment protocols. The mRNA expressions of 92 inflammatory genes were then analyzed. Oxygen at 1.5 atm abs strongly affected many more genes than oxygen at 2.4 atm abs.

Eggum and Hunter [39] experimented with canine mesenchymal stem cells under various levels of pressure, oxygen, glucose and conditioned medium. The culture system showed no cytotoxicity and was able to demonstrate that the proliferation and metabolism of mesenchymal stem cells are sensitive to medium glucose and oxygen concentration and hydrostatic pressure.

The above studies concentrate on hydrostatic pressure effects on neurons and vascular cells as well as gene and stem cell expression. Although these are *in vitro* studies, they cannot be ignored as potential factors regarding the improvements seen in the low hydrostatic sham exposure group as well as the higher hydrostatic treatment exposure group.

A recent publication by Boussi-Gross, et al. [40] used a crossover methodology to avoid a pressurized sham exposure. This study showed statistically significant changes in cognitive function tests and quality of life in both the hyperbaric oxygen group and hyperbaric oxygen after a crossover period. All subjects had an impact etiology, and there was no mention of PTSD confounders. However, it did demonstrate subject perception of improvement using the EQ-50 questionnaire once subjects completed the hyperbaric oxygen exposure. Our study was similar if one views the PCL-M as subject perception of improvement.

Statistical significance and clinical significance

Placebo effect in our previous reports has been considered as why there was no significant statistical difference in this study, and it remains a valid rationale. Subjects were in a non-work environment, with their only job that of participating in the study and continuing any pre-study medical treatment and medications. However, both groups clinically improved. Despite a seemingly reasonable sample size of 48 subjects completing the trial, traditional statistical models found no significant differences between the groups, even though higher proportions of subjects in the treatment group improved. These improvements occurred in a pressure/oxygen spectrum that incorporated the anecdotal pressure of 1.5 atm abs. Thus, it is plausible that a larger sample may be required to see (with statistical significance) an effect between the treatment and sham groups in these models. This underpowered pilot study could have lead to a Type II error. The emphasis on the RROI was therefore examined with interest. The findings in this study from this additional examination identified potential subgroups that may have benefited by the treatment hyperbaric oxygen exposures compared to the sham exposures. This brings us to a growing research area of statistical significance vs. clinical significance.

Jaeschke, Singer and Guyatt [41] first proposed that research results be looked at from not only a distributive perspective but also from the patient's perspective. This they termed the minimal clinically important difference (MCID) as "the smallest difference in score in the domain of interest which patients perceive as beneficial

and which would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management." Since 1989, this has evolved into anchor-based estimates. The choice of anchor is application-specific to the clinical measure and seemingly becomes more refined as research on the clinical measure matures. However, the focus of clinical trial results can also focus on establishing the MCID more so than the minimally detectable change defined by statistical significance [42]. The statistical estimate (which is independent of the psychological MCID) is a change of a 0.5 standard deviation.

In this study, the MCID is best seen in the PCL-M data. The reliable change and statistically significant change are addressed in the National Center for PTSD PCL handbook [43], and their pedigree can be traced back to these concepts. In 1984, Jacobson and Follette [44] defined clinically significant change as "the extent to which therapy moves someone outside the range of the dysfunctional population or within the range of the functional population." In other words, viewing patients entering therapy as part of a dysfunctional population and when departing from therapy as no longer belonging to that population would be considered having significant change. Their rationale is best described in Jacobson's comments:

"First, the tests provide no information on the variability of response to treatment within the sample; yet information regarding within-treatment variability of outcome is of the utmost importance to clinicians. Second, whether a treatment effect exists in the statistical sense has little to do with the clinical significance of the effect. The existence of a treatment effect has no bearing on its size, importance, or clinical significance. Questions regarding the efficacy of psychotherapy refer to the benefits derived from it, its potency, its impact on clients, or its ability to make a difference in peoples' lives. Conventional statistical comparisons between groups tell us very little about the efficacy of psychotherapy" [45].

Jacobson and Truax developed the concept of a reliable change index based on norms and distribution of functional and dysfunctional populations and their overlap or lack thereof as well as the establishment of cutoff points where the dysfunctional individuals improve enough that they fall into the functional population. The reliable change index is an improvement that is unlikely to occur without actual change. Monson and Gradus [46] used Jacobson and Truax's formulas to calculate clinically significant and reliable change in the PCL. In addition, the study's main purpose was to compare the PCL to the Clinician-Administered PTSD Scale and validate Forbes, Creamer and Biddle's [47] study showing high diagnostic accuracy pre- and post-treatment between the provider interview (Clinician-Administered PTSD Scale) and the self-reported (PCL) symptoms. Monson and Gradus revealed significant longitudinal associations between clinician and patient ratings of PTSD symptoms over the course of treatment and also over the course of time in patients who are waiting for treatment when evaluated on a continuous basis. The study also supported their recommended use of brief self-report measures PCL to document the effects of PTSD interventions across treatment in clinical practice, where the administration of independent clinician interviews on multiple occasions is prohibitive [46]. This would be congruent with the use and findings of the PCL-M results in this study. The reader should note the PCL-M in the study used results based on the pre PCL-M 5 guidelines. The new PCL-M 5 for DSM-V was released in January 2014, and the study scores cannot be used interchangeably.

Review of recent studies

This study was the first of four DoD/VA research projects completed, and the specific designs of each project are described in Weaver [48]. Of these studies, only two have any related publications: the U.S. Air Force study and the collaborative venture by the U.S. Navy, Veterans Administration and Virginia Commonwealth University (VCU). Wolf showed neither the PCL-M scores nor the symptoms inventory from ImPACT were significantly different between the sham (1.3 atm abs) and 2.4 atm abs exposure groups, yet both groups had an improvement trend (11). Hyperbaric oxygen also appeared safe, with side effects in TBI subjects at 2.4 atm abs being no different than in the 1.3-atm abs subjects [10].

The U.S. Navy-VA-VCU study exposed all subjects to 2.0 atm abs with three randomized groups:

- sham 10.5% oxygen simulating air at 1.0 atm abs;
- 75% oxygen simulating 1.5 atm abs breathing 100% oxygen; and
- 2.0 atm abs breathing 100% oxygen.

The study used the Rivermead Post-Concussion Symptom Questionnaire (RPQ) as the primary outcome, but also used the PCL-M and other measures as secondary outcomes. The study to date has published three articles, starting with the completion of the hyperbaric exposure series [49], one-week follow-up [50] and three-month follow-up [51].

At the immediate post-exposure series, no significant differences were found between the three groups on any individual symptom inventory items, subscale scores (RPQ-3; RPQ-13) or RPQ-16 (total) scores on the RPQ or PCL-M. RPQ-3 scores represent cognitive symptoms and RPQ-13 represent emotional and somatic symptoms. The one-week follow-up after the hyperbaric exposure series found no immediate beneficial effect of hyperbaric oxygen on cognitive or psychomotor performance at either 1.5 or 2.0 atm abs oxygen compared to the sham air intervention. The three month follow-up found no beneficial effect of hyperbaric oxygen exposure for symptoms, functional status, or cognitive or psychomotor performance at either 1.5 or 2.0 atm abs equivalent oxygen breathing compared to sham intervention.

As all three groups were at 2.0 atm abs, there is no pressure effect between groups. Consequently, any observed changes would be due to oxygen or nitrogen partial pressure differences. In looking at the Rivermead scores (RPQ-3, RPQ-13 and RPQ-16) from baseline to the immediate post-hyperbaric exposure, the scores (pre/post) were as follows:

	RPQ-3	RPQ-13	RPQ-16
sham	5.20/5.10	27.57/27.76	32.81/32.86
1.5 atm	5.04/5.19	24.29/25.38	29.33/30.57
2.0 atm	4.60/4.00	25.83/22.67	30.44/26.67

In observing these data, both the sham and 1.5 atm abs values show an increase (worsening) in scores, with the exception of the 0.1 decrease in the sham RPQ-3. Contrarily, the 2.0 atm abs data show a decrease in RPQ-3, RPQ-13 and RPQ-16 scores immediately after the hyperbaric exposure series. These immediate post-hyperbaric exposure series RPQ-16 data are not plotted in Figure 2 of the three-month follow-up paper. The baseline RPQ-16 values in the Figure 2 plot also do not correlate with the above data values found in the immediate post-series paper.

The use of the PCL-M in the U.S. Navy/VA/UVC study allows some direct comparison to our study. The immediate post-hyperbaric exposure series demonstrated a 6.83 decrease in total composite score from baseline in the 2.0 atm abs group vs. 1.24 and 1.38 in the sham and 1.5 atm abs groups respectively. This indicates a reliable PCL-M change in the 2.0 atm abs group by definition. Our study had a significant change of 10.13 in the 2.4 atm abs group immediately after the hyperbaric exposure series. This suggests a possible dose response of oxygen which should be explored *ad hoc* in the PTSD-diagnosed subjects. The larger decrease in the RPQ-13 scores in the 2.0 atm abs U.S. Navy/VA/UVC study group also represents changes in the emotional and somatic symptoms common in the PTSD cohort.

Calpain, hyperbaric oxygen and traumatic brain injury

Hyperbaric oxygen is an indication in the treatment of acute carbon monoxide poisoning, and Weaver demonstrated that there was a reduction in the rate of delayed neuropsychiatric syndrome in patients who were treated acutely with hyperbaric oxygen [52]. Chang demonstrated that hyperbaric oxygen ameliorates delayed neuropsychiatric syndrome of carbon monoxide poisoning [8]. Lo showed that delayed neuropsychiatric syndrome in carbon monoxide toxicity may be due to the destruction of the myelin coating around neuronal axons that may be slowed by treatment with hyperbaric oxygen [53]. The demyelination effect has been shown by Tofighi to be linked to the expression of a specific protease, calpain [54], and this protease has also been implicated in a similar demyelination of neurons seen in the progress of pathology associated with TBI [55]. We feel demyelination may be the critical similarity between the two clinical conditions and suggested this in our original 2007 protocol. This hypothesis is supported by more recent research such as Ma's review [56] of the role of calpains linked to the dysfunction and degeneration of axons in TBI, spinal cord injury, cerebral ischemia, neurodegenerative diseases and peripheral neuropathies. He concludes that while the direct mechanisms by which transection, mechanical strain, ischemia or complement activation trigger intra-axonal calpain activity are likely different, the downstream effects of unregulated calpain activity may be similar in seemingly disparate diseases.

The capability to measure calpain activity via immunohistochemistry has been demonstrated by Bralic [57] in human TBI patients and more recently by Zhang [58] using anti-GFAP autoantibody levels which correlated with negatively with Glasgow Outcome Score Extended at six months. This presents an opportunity for future research in the potential use of hyperbaric oxygen in more acute TBI cases, such as sports concussions and perhaps preventing chronic TBI.

SUMMARY

Overall, there was no statistical significant difference between the designed sham and hyperbaric oxygen at 2.4 atm abs in cognitive scores from ImPACT and Braincheckers or composite scores in the PCL-M when using ANCOVA and RMANOVA; however, both groups showed improvement in scores and thus a benefit. Given the studies demonstrating hydrostatic pressure effects and results of Boussi-Gross' crossover study, our design could be considered a treatment comparison vs. a true sham with a therapeutic effect from both increased oxygen partial pressure and hydrostatic pressure. A Type II statistical error cannot be ruled out. When comparing subject data using relative risk analysis, 2.4 atm abs hyperbaric oxygen exposures had a beneficial RROI in subjects if started within two years of the last concussive event in subjects with multiple concussive events and within one year in single-event subjects in both ImPACT and Braincheckers. ImPACT also identified benefit in subjects who had two concussive events within 48 hours. Braincheckers identified benefit in subjects who had both impact and blast concussion etiology and who lost consciousness. Individual subtests that demonstrated a beneficial RROI were visual memory and processing in ImPACT and procedural and simple reaction speed as well as accuracy in go-no go and simple reaction times in Braincheckers (ANAM). If further validated in larger studies, these outcomes can provide guidelines in selecting candidates for potential hyperbaric oxygen as an adjunct treatment based on concussion history as well as poor performance on initial scores (or a significant drop from baseline) in the above subtests.

PCL-M showed a beneficial RROI of 2.4 atm abs hyperbaric oxygen exposures in individuals with multiple concussive events, but also in subjects who were exposed to multiple non-symptom-producing blast and impact events. These subjects would intuitively have a higher probability of PTSD, as there would be a sense of danger from those multiple concussive and non-concussive events. Subjects also responded favorably if 2.4 atm abs hyperbaric oxygen therapy was started within two years of the last event and favored individuals who experienced an impact etiology. Hyperbaric oxygen should be considered as a potential adjunct treatment for PTSD particularly if validated in a PTSD population without comorbid TBI.

This pilot study demonstrated no obvious harm, including seizure, observed at the higher dose of 2.4 atm abs for 90 minutes. In clinical settings symptomatic chronic TBI patients are treated for routine indications. These patients can be treated at pressures above 1.5 atm abs, a concern expressed by some HBO_2 providers. The pilot study also demonstrated feasibility in conducting a larger study that can be blinded and randomized and successfully use common neuropsychological computerized tests and questionnaires as evaluation data points. In this report, identified subgroups represent small populations, but one of the goals of this pilot study was to guide research toward populations that are more likely to respond to treatment. We recommended that future studies evaluating hyperbaric oxygen in TBI perform similar concussion histories so a true meta-analysis of subgroup results can validate or refute these preliminary findings. Alternatively, a case could be made that future studies should be aimed at the subgroups that showed the most promise in this pilot study, such as patients within two years of their last TBI event. The Dec 2008 DoD Consensus Meeting on Traumatic Brain Injury and Hyperbaric Oxygen [personal notes 59] was clear that TBI subjects were likely to have PTSD also and that it would be very difficult to separate the two diagnoses. *Post-hoc* analysis in this study, however, identifies potential hyperbaric oxygen and hydrostatic pressure effects on symptoms associated with both diagnoses. Scorza's analysis of our study demonstrated significant improvements in subjects who had a diagnosis of PTSD per the PCL-M. This was supported by the subgroup improvement in the PCL-M of those subjects who are more likely to have PTSD from experiencing multiple life-threatening events.

Additional analysis of our data as well as additional studies within civilian institutions, the DoD and the Department of Veterans Affairs need to continue to validate or refute this study's findings. For example, we have yet to analyze the wealth of information obtained in the pre-, post- and six-week follow-up history and physicals including clinical interviews on subject symptoms patterned after Pardini and should reassess our previous symptoms publication regarding concussion history and potential pressure effects. It is not coincidence that the horizontal symptom ovals pertain to TBI and the vertical ovals relate to PTSD symptoms. Another area would be changes in medications by home providers between the post-hyperbaric series and the six-week follow-up. In addition, our data should be combined with those of the other DoD/Veterans Affairs studies for larger analysis as well as follow-up surveys to determine endurance of findings. One final area to explore is the potential use of hyperbaric oxygen in acute concussion, particularly in athletics, where professional, collegiate and high school teams already do preseason cognitive tests, such as ImPACT. Concussed players could be directly compared in time to return to baseline between hyperbaric-treated and standard-of-care groups, with possible crossover similar to Boussi-Gross.

Jaeschke's definition and philosophy regarding his MCID are remarkably similar to the AHRQ 2003 report evaluating the use of hyperbaric oxygen for TBI. The recommendations section stated:

"If there is a 1 percent chance that the treatment works, a rational decision maker would try it – there is a potential gain and no potential loss. On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it" [9].

Our previous publication from the study demonstrated hyperbaric exposures as high as 2.4 atm abs were safe and comparable in side effects to the sham in the TBI population. This is important in that this pressure is used as a standard treatment for patients worldwide on a daily basis, many of whom may have had TBI. Subgroup analysis of cognitive changes and PCL-M results regarding PTSD demonstrated a relative risk of improvement using 2.4 atm abs hyperbaric oxygen. There is a potential gain and no potential loss. The VA/Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm" [2]. Hyperbaric oxygen therapy for mild traumatic brain injury and PTSD should be considered a legitimate adjunct therapy if future studies demonstrate similar findings or show comparable improvement to standard-of-care or research-related treatment modalities.

Finally, we advocate from the findings in this study, both the clinically significant and the statistically non-significant, that the proper design and execution of a large clinical trial including a proper treatment, control and sham group to be conducted to finally provide the cornerstone evidence as to the merits of hyperbaric treatment for improved cognitive functioning in subjects with traumatic brain injury.

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Disclaimer

The opinions expressed in this document are solely those of the authors and do not represent an endorsement by or the views of the United States Air Force, the Department of Defense, or the United States Government.

Conflict of interest

The authors report no conflict of interest with this submission. ■

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