

Case control study: hyperbaric oxygen treatment of mild traumatic brain injury persistent post-concussion syndrome and post-traumatic stress disorder

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Abstract

Mild traumatic brain injury (TBI) persistent post-concussion syndrome (PPCS) and post-traumatic stress disorder (PTSD) are epidemic in United States Iraq and Afghanistan War veterans. Treatment of the combined diagnoses is limited. The aim of this study is to assess safety, feasibility, and effectiveness of hyperbaric oxygen treatments (HBOT) for mild TBI PPCS and PTSD. Thirty military subjects aged 18–65 with PPCS with or without PTSD and from one or more blast-induced mild-moderate traumatic brain injuries that were a minimum of 1 year old and occurred after 9/11/2001 were studied. The measures included symptom lists, physical exam, neuropsychological and psychological testing on 29 subjects (1 dropout) and SPECT brain imaging pre and post HBOT. Comparison was made using SPECT imaging on 29 matched Controls. Side effects (30 subjects) experienced due to the HBOT: reversible middle ear barotrauma ($n = 6$), transient deterioration in symptoms ($n = 7$), reversible bronchospasm ($n = 1$), and increased anxiety ($n = 2$; not related to confinement); unrelated to HBOT: ureterolithiasis ($n = 1$), chest pain ($n = 2$). Significant improvement (29 subjects) was seen in neurological exam, symptoms, intelligence quotient, memory, measures of attention, dominant hand motor speed and dexterity, quality of life, general anxiety, PTSD, depression (including reduction in suicidal ideation), and reduced psychoactive medication usage. At 6-month follow-up subjects reported further symptomatic improvement. Compared to Controls the subjects' SPECT was significantly abnormal, significantly improved after 1 and 40 treatments, and became statistically indistinguishable from Controls in 75% of abnormal areas. HBOT was found to be safe and significantly effective for veterans with mild to moderate TBI PPCS with PTSD in all four outcome domains: clinical medicine, neuropsychology, psychology, and SPECT imaging. Veterans also experienced a significant reduction in suicidal ideation and reduction in psychoactive medication use.

Key words: hyperbaric oxygen; traumatic brain injury; persistent post concussion syndrome; post traumatic stress disorder; single photon emission computed tomography; cognitive assessment; brain injury treatment; combat veterans

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INTRODUCTION

Blast-induced traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) remain the two most common afflictions of U.S. military service personnel who served in the Iraq and Afghanistan Wars. A Rand Report¹ estimates that 300,000 (18.3%) of 1.64 million military service members who have deployed to these war zones have PTSD or major depression and 320,000 (19.5%) have experienced a TBI. Overall, approximately 546,000 have one of the three diagnoses and 82,000 have symptoms of all three [Note: For the present study the authors are using the Rand Report¹'s definitions of TBI (from the Centers for Disease Control and Prevention 2008): “a trauma to the head that either temporarily or permanently disrupts the brain’s function,” mild TBI (mTBI): “a Glasgow Coma Scale of 13–15... (The Glasgow Coma Scale is a 15 point scale that measures a patient’s best eye-opening, motor, and verbal responses),” and PTSD: “an anxiety disorder that occurs after a traumatic event in which a threat of serious injury or death is experienced or witnessed and to which the individual’s response involved intense fear, helplessness, or horror.” mTBI disruption of brain function lasting longer than 3–6 months is the persistent post-concussion syndrome (PPCS), according to Diagnostic and Statistical Manual IV-Text Revised (DSM-IV-TR) criteria listed in the Methods Section. PPCS is synonymous with the diagnosis of TBI used in military medical reports quoted herein].

The frequency of the combined diagnoses in veterans of mild TBI and PTSD has been estimated at 5–7%.² With a probable diagnosis of mild TBI the combined diagnosis incidence rises to 33–39%.² A Walter Reed Army Institute of Research post-deployment survey of 4,618 soldiers reported 15.2% of injuries with history of loss of consciousness or altered mental status.³ That study also found that 43.9% of those with history of loss of consciousness and 27.3% of those with history of altered mental status met criteria for PTSD. Separating the two diagnoses of PPCS and PTSD, however, has been very difficult. When adjustments were made for PTSD and depression by logistic regression analysis, the only symptom unique to mild TBI was headache. Due to this difficulty in differentiation no attempt was made to separate the two diagnoses in this study based on symptoms alone.

Evidence-based treatment for PTSD exists, but problems with access to and quality of treatment have been problematic in the military.¹ Treatment of the chronic symptomatic manifestation of mild TBI, the PPCS, is limited. Most of TBI rehabilitation and medical management is based primarily on expert opinion.¹ Treatment consists of off-label use of Food and Drug Administration (FDA) blackbox-labeled psychoactive medications, counseling, stimulative,

and adaptive strategies.

Hyperbaric oxygen therapy (HBOT) is the use of increased atmospheric pressure and hyperoxia as drugs to treat disease pathophysiology through gene expression and suppression.^{4,5} Treatment effects are a function of dose and timing of intervention in the disease process. Historically, HBOT doses of 203–304 kPa have been applied to 15 typically reimbursed acute or chronic wound and infection diagnoses.^{5–7} Lesser doses have been used mainly for chronic neurological conditions.⁸

Oxygen toxicity^{9,10} is a concern in the testing of hyperbaric oxygen to treat PPCS and PTSD. The most extreme form of oxygen toxicity is a grand mal seizure.^{9,10} A study of HBOT on sub-acute moderate to severe TBI at 203 kPa¹¹ reported a 9% seizure rate. Less severe toxic/harmful effects¹² were demonstrated in the Wolf et al.¹³ blast-induced mTBI/PPCS study using a dose of 243 kPa. At doses less than 203 kPa, side effects and toxicity in chronic brain injury patients have been noted only with prolonged courses of HBOT, i.e., 70–500 treatments.¹⁴

Low-pressure HBOT has been applied to chronic traumatic brain wounding in moderate and severe TBI cases^{15–23} and replicated in a controlled animal study.²⁴ The first HBOT-treated cases of mild TBI were in patients with blast-induced PPCS with²⁵ or without²⁶ PTSD. Clinical and cognitive improvements in a series of subsequent off-label cases in 2008 prompted the present study to assess safety and feasibility, and assess outcomes with standard cognitive testing and functional brain imaging. In all of the early cases and those of other neurological disorders the improvements noted after HBOT were captured on single photon emission computed tomography (SPECT) brain imaging with an improvement in the texture of the scans manifest as a visual smoothing of an abnormal pattern of brain blood flow to the pattern of blood flow seen in neurologically normal people. This study attempted to capture this smoothing pattern mathematically with a texture analysis. In addition, since the publication of the preliminary results of the present study²⁷ other authors have reported similar^{13,28–30} results with similar^{28,30} and different^{13,29} doses of hyperbaric therapy, and conflicting results,^{12,29,31,32} using different doses of hyperbaric therapy. The prior report of preliminary data²⁷ noted that the findings needed confirmation with larger numbers and a stronger design. This report confirms and strengthens the previous findings with a larger number, a 6-month symptom follow-up, and the addition of a SPECT control group.

SUBJECTS AND METHODS

Design

This is a prospective case-control institutional review

board approved pilot study. The original design was for 15 active duty or retired military service members with mild-moderate blast TBI PPCS and 15 service members with mild-moderate TBI PPCS and PTSD. Early recruitment was dominated by patients with the combined diagnoses so the study design was changed to recruitment of the first 30 subjects with either PPCS or PPCS with PTSD. The final treated subject cohort was matched to a group of anonymized SPECT imaged population controls from a previous study (unpublished data).

The study methods were described in a previous report.²⁷ Subjects were screened, enrolled, examined, completed symptom questionnaires, neuropsychological and psychological testing, and SPECT imaged before and after the first HBOT and then within 5 days after the full series of twice a day, 5 days per week HBOTs at 152 kPa/60 minutes. Six months following the 40th HBOT, subjects responded to a

phone questionnaire. Subject flow is shown in **Figure 1**.

Subjects

There were 30 active duty or retired military service men and women (18–65 years old) with one or more mild-to-moderate blast TBIs characterized by loss of consciousness that were a minimum of 1 year old and occurred after 9/11/01. All subjects were diagnosed by military or civilian specialists with chronic TBI/PPCS or TBI/PPCS/PTSD. Loss of consciousness (LOC) was estimated by each patient and the principal investigator (P.I.) based on patient recollection, details of the event, and bystander reports to patient. When anterograde memory loss exceeded 30 minutes, could not be distinguished from LOC, and medical records were not available subjects were deemed moderate TBI. Prior diagnoses of TBI/PPCS and PTSD were confirmed or refuted by using clinical interviews, symptom lists, the Rivermead Post Concussion Symptoms Questionnaire³³ (PCS; > 3 on at least 3 questions),³⁴ the PTSD Checklist-Military³⁵ (total > 50),¹ and Diagnostic and Statistical Manual-IV Text Revised (DSM-IV TR) criteria for the diagnoses.³⁶ All subjects and population Normals gave informed consent under approval of the Louisiana State University Institutional Review Board, LSU IRB #7051 (ClinicalTrials.gov identifier: NCT00760734) and LSU IRB #3511, respectively.

The DSM-IV-TR criteria used for diagnosis of PPCS was:

1) a history of head trauma that has caused significant cerebral concussion;

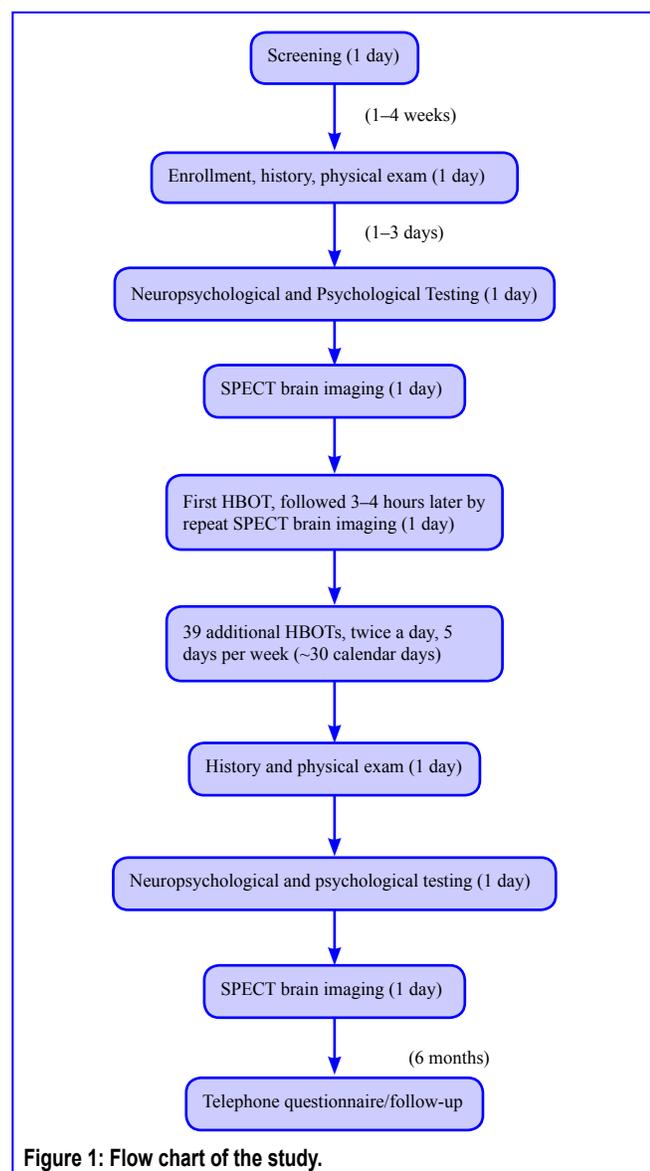
2) evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention (concentrating, shifting focus of attention, performing simultaneous cognitive tasks), or memory (learning or recalling information);

3) three or more of the following occur shortly after the trauma and last at least 3 months: a) Becoming fatigued easily, b) Disordered sleep, c) Headache, d) Vertigo or dizziness, e) Irritability or aggression with little or no provocation, f) Anxiety, depression, or affective lability, g) Changes in personality (e.g., social or sexual inappropriateness), h) Apathy or lack of spontaneity;

4) the symptoms in criteria 2) and 3) have their onset following head trauma or else represent a substantial worsening of pre-existing symptoms;

5) the disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning (in school-aged children, the impairment may be manifested by a significant worsening in school or academic performance dating from the trauma);

6) the symptoms do not meet criteria for dementia due to head trauma and are not better accounted for by another





mental disorder (*e.g.*, amnesic disorder due to head trauma, personality change due to head trauma).³⁶

Exclusion Criteria: Subjects with significant pulmonary disease, medical co-morbidities with significant risk for HBOT or that confounded testing, claustrophobia, pre-morbid neurological diagnoses, and substance abuse were excluded. Subjects were counseled to give maximal effort and effort-tested pre-HBOT, but those who scored below accepted cutoffs were not excluded from the study. Bronchospasm unresponsive to medication was the sole criteria for subject removal.

Symptom scoring

Patient-prioritized symptoms and symptoms from the P.I.'s standard questionnaire²⁷ (**Additional Table 1**) were recorded pre-treatment and scored by the subject after the last HBOT as “better” (improved), “worse” (deteriorated), or “same” (no change). Six months following the last HBOT subjects were queried by phone about the status of all symptoms as “better, worse, or same” compared to pre-HBOT and post-40 HBOTs.

Psychometric testing

Outcome variables are listed in **Additional Table 1** and include: Wechsler Adult Intelligence Scale-IV Full Scale IQ (WAIS-IV),³⁷ Wechsler Abbreviated Scale of Intelligence (WASI),³⁸ Wechsler Memory Scale-IV Delayed Memory Index and Visual Working Memory Index (WMS-IV),³⁹ Rivermead Post Concussion Symptom Questionnaire (RPCSQ),³³ Test of Variables of Attention (TOVA),⁴⁰ the Stroop Test,⁴¹ Finger Tapping and Grooved Pegboard Tests,⁴² the Paragraph memory subtest of the Rivermead Behavioural Memory Test,⁴³ PTSD Checklist-Military (PCL-M),³⁵ the Perceived Quality of Life (PQOL),⁴⁴ Generalized Anxiety Disorder Scale (GAD-7),⁴⁵ the Patient's Health Questionnaire (PHQ-9),⁴⁶ and the Percent Back To Normal Ratings (PBTN)⁴⁷ for cognitive, emotional, and physical functioning. These measures were administered before and after completing the 40 HBOT treatments. The Michigan Alcohol Screening Test (MAST),⁴⁸ Drug Abuse Screening Test (DAST),⁴⁹ Green Word Memory Test (WMT),⁵⁰ Wechsler Test of Adult Reading (WTAR),⁵¹ the Combat Experience Scale (CES),⁵² and the Disability Rating Scale⁵³ were administered pre-treatment only. Choice of tests was guided by past experience and the medical literature. Practice and test/retest effects were minimized or accounted for by using alternate tests, *e.g.* WAIS-IV on pre-test and WASI post-test, and by including the Reliable Change Analysis on the WMS-IV primary outcome variables of Delayed Memory Index and Visual Working

Memory Index (the first 5 subjects were tested with the WAIS III, after which the newly issued WAIS IV was used for the remaining 26 subjects).

SPECT brain blood flow imaging

Subjects underwent SPECT brain blood flow imaging on a Picker Prism 3000 XP Triple-Head gamma camera system (Cleveland, Ohio, USA) before, within 3–4 hours after the first HBOT, and within five days after the 40th HBOT. Acquisition, processing, and formatting were previously described.²⁷ Control subjects were imaged between 1998 and 2002 under identical conditions with the same radiopharmaceutical/dose in the same nuclear medicine department on an earlier model Picker Prism 3000 XP Triple-Head gamma camera system. The raw data from their scans was re-processed and re-formatted by the same technologist in identical fashion to treated subjects using the software on the later model Picker XP.

SPECT texture analysis

Transverse processed images were analyzed with open source DICOM software package OsirixTM, using a first order texture analysis of count histograms⁵⁴ to register improvements in heterogeneity of blood flow⁵⁵ seen in previously treated chronic TBI subjects.¹⁵ Mean counts/pixel (MCP), standard deviation of counts/pixel, and coefficient of variation (CV) (standard deviation as a percent of mean) of counts/pixel were measured for five gray and two white matter circular regions of interest (ROIs) at designated sites in each hemisphere on all three scans for each patient and then separately for the individual scans for the Controls.²⁷ The nuclear technologist was not blinded to group or sequence of scans. Averages were determined for each ROI of each measured parameter for Control and pre-HBOT scans, compared to each other, and to post-1 and post-40 HBOT scans. Statistical analysis was performed as described below. A decrease in CV (improvement in texture) was the primary SPECT outcome.

SPECT three-dimensional surface reconstruction

Three-dimensional reconstruction was performed by a single nuclear technologist using the method developed by Picker International using Picker software whereby brain blood flow is computer indexed to frontal lobe blood flow. A frontal lobe surface defect was identified on a selected transverse slice. Processed/filtered transverse slices were then featured with a 100% window such that all pixels render a white image. Counts were slowly subtracted by decreasing the window threshold until the defect was visible as a full thickness black defect in the contour of the cortex. As the defect emerged and was registered in proper anatomic proportion to the rest of frontal cortical



blood flow the numerical window level was taken as the determination threshold for the entire brain. Three separate determinations were made for each scan and the final threshold taken as an average of the three determinations. The technologist was blind to the final image reconstruction due to software restrictions that only allow threshold determination, but not blind to dates of scans. Color is aesthetic.

HBOT

HBOT was performed in monoplace hyperbaric chambers on a protocol the investigators developed in 1989.¹⁵ Patients were compressed and decompressed at 1–2 pound per square inch on 100% oxygen to 152 kPa for 60 minutes total dive time, twice/day with a 3–4 hours surface interval, 5 days/week, for 40 HBOTs.

Statistical analysis

Values of psychometric tests were acquired pre-HBOT and post-40 HBOTs; SPECT parameters were acquired pre-HBOT, post-1 HBOT, and post-40 HBOTs. For each SPECT ROI at each time point mean, standard deviation, median, range (minimum and maximum), and 95% confidence interval around the estimated mean were calculated for mean of counts/pixel, standard deviation of counts/pixel, and CV of counts/pixel. Changes in psychometric and SPECT parameters between pairs of time points (pre-HBOT to post-1-HBOT, pre-HBOT to post-40-HBOTs, and post-1-HBOT to post-40-HBOTs) were similarly summarized, using the Tinn-R version 2.3.7.1 (<http://tinn-r.soft112.com>), with the inclusion of a nominal *P*-value indicating whether or not the mean change was significantly different from zero. The *P* values were obtained by the paired Student *t* test if the changes were nearly normally distributed, or by the non-parametric Wilcoxon Signed-Ranks test if the changes were significantly non-normally distributed by the Anderson-Darling test. No multiplicity adjustments were applied to *P* values in this exploratory study; all *P* values should be considered descriptive, not inferential. One subject who withdrew before completion of treatment and post-treatment testing was included in the demographic data and safety/feasibility analysis, but excluded from the per-protocol analysis (outcome testing). Reliable Change Score analysis (Wechsler Advanced Clinical Practice software) to assess practice and/or test-retest effect was performed on Visual Working Memory Index (VWMI) and Delayed Memory Index (DMI) of the Wechsler Memory Scale-IV.³⁹

RESULTS

Demographics of samples

Recruitment began 9/17/2008 and ended 8/15/2010 with the enrollment of 30 subjects. Six-month followup ended

Table 1: Subject demographics of mild traumatic brain injury persistent post-concussion syndrome with or without post-traumatic stress disorder

Patient characteristics	Safety population (all enrolled subjects)
Number of subjects	30
Sex	28 male, 2 female
Average age (years)	30.3 (21–51)
Race	1 Asian, 1 Black, 3 Hispanic, 25 Caucasian
Service	15 army, 15 marine
Duty	11 active, 19 retired
TBI-to-HBOT interval (years)	3.35 (1.25–5.83)
Duration of LOC (minutes)	Mean = 1.3 for 25 subjects (< 1–10 minutes) ^a
Severity of TBI	25 mild, 5 moderate
Service at time of LOC (years)	6.0 (0.75–25)
Blast TBIs with LOC/altered LOC	2.3 (1–7)
Prior TBIs (range)	1.24 (0–10)
Diagnosis (TBI, PTSD)	3T, 27 T/P
RPCSQ ³³ score (scale: 0–64)	36.9 (14–52)
PCL-M ³⁵ score (scale: 17–85)	63.4 (21–84)
CES ⁵²	30.0 (9–58)
HBOTs/days (not including 1 dropout)	39.7 HBOTs (38–40)/30.1 days (23–44)
MAST ⁴⁸ score (scale: 0–22)	1.8 (0–5)
DAST ⁴⁹ score (scale: 0–20)	0.67 (0–3)
Psychoactive medication	23/30 (77%)
Tobacco (packs/d)	0.26 (0–2)
DRS ⁵³ (scale: 0–29)	1.6 (0–3)
PBTN ⁴⁷ pre-study	46% (5–80)
Pre-TBI estimated IQ	105.8 (93–119)
Years of education	13.1 (9–19)
Imaging post TBI (CT or MRI)	22 normal, 8 abnormal

Note: Numerical variables are summarized as mean and range (minimum to maximum). IQ: Intelligence quotient; LOC: loss of consciousness; TBI to HBOT: traumatic brain injury to hyperbaric oxygen therapy; PTSD: post traumatic stress disorder; RPCSQ: Rivermead Post Concussion Symptom Questionnaire; PCL-M: PTSD Check List - Military; CES: Combat Experience Scale; MAST: Michigan Alcohol Screening Test; DAST: Drug Abuse Screening Test; DRS: Disability Rating Scale; PBTN: Percent Back to Normal Rating Scales. ^a Excluding 5 subjects (1, 2, 4.5, 9, and 9 hours).

3/23/2011. Sample demographics are reported in **Table 1** (Subject Demographics) for the 30 enrolled subjects and **Table 2** (Subject and Control Characteristics) for the 29 subjects who completed the protocol along with 29 matched SPECT Controls. One subject withdrew from the study due to an ear infection, bronchospasm, and middle ear barotrauma; he was excluded from all data analyses. The only significant difference between subjects and Controls was years of formal education (greater for Controls); however, many study subjects had military and trade school education/training that was not counted.

**Table 2: Subject and control characteristics (29 subjects)**

Item	Subjects	Controls	P value
Age (years)	30.4±7.5 (29) 29 (21–51)	33.6±8.3 (29) 34 (18–47)	0.133
Sex			1.000
Female	2 (7%)	2 (7%)	
Male	27 (93%)	27 (93%)	
Tobacco (Packs/day)	0.27±0.50 (29) 0 (0–2)	0.26±0.41 (29) 0 (0–1.14)	0.922 (np)
Alcohol (drinks/day)	0.62±0.99 (29) 0 (0–3)	0.10±0.15 (29) 0 (0–0.57)	0.831 (np)
Education (years)	13.02±2.01 (29) 12 (9–19)	14.06±1.86 (29) 14 (11–17)	0.041 (np)
Handed			1.000
Left	2 (7%)	2 (7%)	
Right	27 (93%)	26 (90%)	
Unknown		1 (3%)	
Race			0.124
Asian	1 (3%)	0 (0%)	
Black	1 (3%)	4 (14%)	
Hispanic	3 (11%)	0 (0%)	
White	24 (83%)	25 (86%)	

Note: Numerical variables are summarized as mean and range (minimum to maximum). A value of $P < 0.05$ (in bold) is considered statistically significant.

Symptoms

Symptom outcomes immediately and 6 months post treatment are reported in **Table 3** (symptoms before, immediately after, and 6 months after treatment). Dizziness, present in only 34% of subjects, was the most responsive of all symptoms, improving in 100% of subjects. The 75–100% of the 29 subjects reported problems with thinking, low energy, headaches, depression, mood swings, short-term memory loss, and a disruption of their sleep; 73–93% of these subjects experienced improvement after 40 HBOTs. Decreased hearing and tinnitus were the least responsive symptoms. The 28 of 29 subjects (97%) responded to 6-month phone follow-up and reported further improvement in 14/18, deterioration in 3/18, and no change in 1/18 symptom(s) in **Table 3**. Fifty percent (11/22) of subjects who were on psychoactive or analgesic prescription medication before HBOT decreased or discontinued their medication usage during HBOT; four others discontinued their medication prior to treatment and were able to maintain their abstinence from medication by the end of treatment. One subject increased narcotic medication due to worsened back pain and another subject increased Trazodone for sleep. Two other subjects restarted or transiently initiated benzodiazepines.

Side effects

Due to the HBOT were: 1) mild reversible middle ear

Table 3: Symptoms of mild traumatic brain injury persistent post-concussion syndrome with or without post-traumatic stress disorder before, immediately, and 6 months after treatment

Ranking of subjects' symptoms (Ss)	Before HBOT (% of Ss Reporting)	After HBOT (% of Ss "Better")	6-month follow-up (% of Ss "Better")
Thinking/cognition	100	90	96
Low energy	100	86	93
Headache	97	93	86
Depression	90	92	87
Mood swings	86	84	96
Short-term memory loss	83	83	91
Sleep disruption	76	73	80
Short temper	72	90	95
Imbalance	69	65	88
Decreased hearing	69	10	22
Speech problems	62	78	87
Tinnitus	58	47	56
Photophobia	55	50	64
Paresthesias	48	57	60
Decreased vision	48	64	71
Arthralgias	45	54	22
PTSD symptoms	34	60	75
Dizziness	34	100	100

Note: HBOT: Hyperbaric oxygen therapy; PTSD: post traumatic stress disorder; "Better" means improved.

barotrauma (MEBT) ($n = 6$), five of these at the outset of upper respiratory infections, 2) transient deterioration in some symptoms that resolved over the next 4–6 HBOTs ($n = 7$), 3) anxiety associated with exacerbation of PTSD (2 subjects, one of which had chest pain/gastroesophageal reflux), and 4) bronchospasm ($n = 1$). Increased anxiety was not due to confinement. Side effects unrelated to the HBOT were: 1) non-cardiac chest pain ($n = 2$), 2) recurrent ureterolithiasis ($n = 1$). Four of these side effects (anxiety-2, exacerbation of headache-1, and ureterolithiasis-1) were considered significant adverse events per protocol definition due to a hospital emergency department visit. Anxiety was treated with re-institution of clonazepam in one subject and a time-limited lorazepam prescription in the other. One subject, bronchospasm patient above, dropped out due to a bullous myringitis, and time limitations in New Orleans. Eleven subjects experienced protocol breaks due primarily to adverse events (above); 10 of these 11 finished the protocol.

Psychometric measures

A summary of pre- to post-HBOT neuropsychological (IQ, memory, attention) and psychological (PTSD, depression,

**Table 4: Summary of pre- to post-HBOT neuropsychological and psychological outcomes**

Item	Pre-HBOT	Post 40 HBOTs	Change	P-value (95% CI)
WAIS-IV Full Scale IQ	97.9±13.6, 98 (66 – 126)	112.1±9.9, 112 (92 – 129)	14.2±10.3, 15 (–9 – 47)	P < 0.001 (10.4 – 18.0)
WAIS-IV Delayed memory	94.0±16.0, 94 (67 – 125)	109.2±17.0, 107 (80 – 153)	15.2±13.9, 17 (–19 – 38)	P < 0.001 (10.0 – 20.4)
WAIS-IV Working memory	96.3±15.4, 94 (67 – 131)	107.6±15.0, 105 (80 – 136)	11.3±10.5, 10 (–15 – 32)	P < 0.001 (7.4 – 15.2)
Stroop C/W Interference	90.0±18.2, 86 (63 – 146)	100.9±14.5, 99 (67 – 136)	10.9±12.2, 10 (–10 – 39)	P < 0.001 (6.3 – 15.5)
TOVA				
Inattention	69.5±29.4, 69 (40 – 109)	77.5±28.6, 91 (40 – 109)	8.0±27.8, 0 (–62 – 61)	P = 0.134 (–2.4 – 18.4)
Impulsivity	86.3±24.7, 90 (40 – 123)	98.2±22.7, 107 (40 – 119)	11.9±20.2, 8 (–25 – 60)	P = 0.004 (4.4 – 19.4)
Reaction time	95.1±26.5, 90 (40 – 156)	98.6±22.3, 103 (43 – 159)	3.5±18.2, 5 (–32 – 43)	P = 0.312 (–3.3 – 10.3)
Variability of RT	66.3±29.8, 47 (40 – 135)	74.9±26.6, 80 (40 – 127)	8.6±25.3, 8 (–70 – 48)	P = 0.078 (–0.8 – 18.0)
Rivermead paragraph	8.1±3.4, 8 (0 – 14)	7.2±3.9, 7 (0 – 16)	–0.9±4.6, –1 (–14 – 8)	P = 0.324 (–2.6 – 0.8)
Finger tap				
Dominant	90.2±15.0, 92 (55 – 118)	96.7±14.6, 98 (55 – 130)	6.4±16.0, 5 (–20 – 68)	P = 0.040 (0.4 – 12.4)
Nondominant	88.9±16.9, 91 (40 – 118)	93.3±20.2, 94 (40 – 130)	4.5±14.7, 1 (–18 – 57)	P = 0.111 (–1.0 – 10.0)
Grooved PegB				
Dominant	87.7±17.8, 88 (55 – 124)	98.9±15.9, 98 (65 – 129)	11.2±13.9, 9 (–14 – 33)	P < 0.001 (6.0 – 16.4)
Nondominant	85.5±19.9, 86 (40 – 120)	89.7±18.5, 91 (40 – 118)	4.2±13.6, 3 (–30 – 36)	P = 0.105 (–0.9 – 9.3)
GAD-7 Anxiety	13.4±6.0, 14 (1 – 21)	8.0±5.1, 7 (0 – 21)	–5.4±5.9, –5 (–14 – 4)	P < 0.001 (–7.6 to –3.2)
PHQ-9 Depression	16.5±6.2, 18 (2 – 27)	8.6±5.6, 8 (0 – 22)	–7.9±6.8, –7 (–21 – 5)	P < 0.001 (–10.4 to –5.4)
PTSD Checklist-Military	63.4±15.9, 68 (21 – 84)	46.8±16.5, 46 (17 – 81)	–16.6±16.2, –16 (–54 – 10)	P < 0.001 (–22.6 to –10.6)
Rivermead Post Con Sx Q	37.0±9.2, 39 (14 – 52)	23.5±12.1, 23 (0 – 49)	–13.5±10.4, –13 (–38 – 12)	P < 0.001 (–17.4 to –9.6)
Quality of Life	79±39, 74 (3 – 162)	108±42, 117 (22 – 166)	28±32, 24 (–37 – 96)	P < 0.001 (16.1 – 39.9)
% Back to normal				
Cognitive	48.3±19.6, 50 (0 – 85)	68.7±19.2, 75 (30 – 95)	20.4±17.4, 15 (–10 – 50)	P < 0.001 (13.9 – 26.9)
Physical	45.8±23.0, 45 (0 – 90)	66.5±18.9, 70 (20 – 95)	20.7±16.2, 20 (–10 – 55)	P < 0.001 (14.7 – 26.7)
Emotional	32.8±20.7, 30 (0 – 90)	63.8±21.7, 70 (20 – 98)	31.1±18.9, 30 (5 – 80)	P < 0.001 (24.0 – 38.2)

Note: Data are expressed as the mean ± variance (standard deviation), Mode (Range: minimum to maximum). A value of $P < 0.05$ (in bold) is considered statistically significant. HBOT: Hyperbaric oxygen therapy; CI: confidence interval; WAIS-IV: Wechsler Adult Intelligence Scale-IV; IQ: Intelligence Quotient; Stroop C/W: Stroop Color/Word; TOVA: Test of Variables of Attention; Variability of RT: Variability of Reaction Time; Grooved PegB: Grooved PegBoard; GAD-7: General Anxiety Disorder Scale-7; PHQ-9: Personal Health Questionnaire-9; PTSD Checklist Military: Post-Traumatic Stress Disorder Checklist Military; Rivermead Post Con Sx Q: Rivermead Post Concussion Symptom Questionnaire.

Quality of Life) outcomes are shown in **Table 4** (Summary of pre- to post-HBOT neuropsychological and psychological outcomes). Significant improvement was recorded on 7 of 13 cognitive measures, one measure showed a trend toward improvement, and the other 5 showed no significant change.

Full Scale IQ, Visual Working Memory, Delayed Memory, and Stroop Test showed the largest improvements at $P < 0.001$, and one measure of attention improved, TOVA Impulsivity ($P = 0.004$). Reliable Change Score analysis on the 24 subjects with WMS IV showed significant changes in Visual Working Memory Index ($P = 0.003$) and Delayed Memory Index ($P = 0.029$)

Subjects experienced significant improvement in anxiety, depression, post-concussion symptoms, and self-assessed cognitive, physical, and emotional functioning. After HBOT 12 of 23 subjects (52%) no longer met the PCL-M threshold criteria for diagnosis of PTSD,¹ experiencing an average 18.8-point reduction in the PCL-M. Ten of

12 subjects who expressed suicidal ideation prior to the HBOT did not express suicidal thoughts after treatment (McNemar's Test; $P = 0.012$). One subject with anxiety and an adverse event (emergency department visit for increased anxiety) during treatment had increased suicidal ideation after treatment. Eighteen of the 24 subjects (75%) who indicated significant anxiety on several items of the GAD-7 before treatment were no longer anxious after treatment (McNemar's Test; $P < 0.0001$). One subject who was not anxious pre-treatment expressed increased anxiety post-treatment.

Four subjects failed the Green Word Memory effort test (score < 82.5% for the 3 primary subtests), however, their pre-HBOT PCL-M scores were significantly higher than the other 25 subjects (80 vs. 61, $P = 0.022$). Re-analysis of demographic data (**Table 2**) and **Table 4** data without these 4 subjects (**Additional file 1**) changed the Finger Tapping Dominant Hand result from significantly positive to a positive trend and the TOVA Variability RT from



a positive trend to non-significant, and showed that the subjects who failed the WMT had a greater delay to treatment and greater increase in FSIQ after HBOT than those who passed the WMT.

Medication increase/decrease or sleep improvement during/immediately after HBOT and sleep improvement 6 months after HBOT had minimal effect on outcome instruments (**Additional file 2**). Contribution of moderate TBI subjects to the data pool was analyzed in **Additional file 3**. A greater percentage of moderate TBI subjects were Asian or Black and decreased the dosage or discontinued their psychoactive medications by the conclusion of HBOT than the mild TBI subjects.

SPECT brain blood flow imaging

Significantly and near-significantly different values for SPECT MCP and CV between veterans pre-HBOT and Controls, changes in veteran SPECT MCP and CV after one and 40 HBOTs, and changes in veterans SPECT MCP and CV after 1 and 40 HBOTs compared to Controls were abstracted from full data sets in **Additional files 4, 5** and presented in **Tables 5–7**.

Compared to Controls, brain blood flow (MCP) and

texture (CV) in veterans pre-HBOT (**Table 5**) were worse, giving the visual appearance of a coarsely heterogeneous pattern. After 1 and 40 HBOTs veterans' SPECT texture improved while blood flow improved only after one HBOT, (**Table 6**), demonstrating the more normal visual smoothing pattern. Compared to Controls (**Table 7**), abnormal veterans' white matter blood flow pre-HBOT improved after 1 and 40 HBOTs, becoming statistically indistinguishable from Controls, while abnormal texture improved after 1 and 40 HBOTs in all eight abnormal ROIs, becoming statistically indistinguishable from Controls in 75% of abnormal ROIs. In addition, after 1 and 40 HBOTs veterans showed improved texture in ROIs that were not significantly different from Controls pre-HBOT. Overall, after 1 and 40 HBOTs veterans' abnormal SPECT brain scans showed a progression to a more normal visually smooth pattern of blood flow.

Radar graphs of SPECT data from **Additional file 4**, from which *P* values in **Table 7** are derived, are presented in **Figure 2**. A visual representation of the texture change towards a normal pattern of blood flow on the radar graphs for a sample veteran before and after HBOT compared to a sample Control subject is presented in both transverse slices and three dimensional surface reconstructions in **Figure 3**.

Table 5: Brain blood flow and texture assessment of brain blood flow in veterans compared to Controls

Region of interest	Mean counts per pixel (MCP)	Coefficient of variation (CV)
Left Gray 030	0.374 (–218 – 83)	0.647 (–0.52 – 0.83)
Left Gray 060	0.251 (–248 – 66)	0.708 (–0.54 – 0.79)
Left Gray 090	0.640 (–188 – 116)	0.310 (–1.32 – 0.43)
Left Gray 120	0.441 (–214 – 95)	0.783 (–0.76 – 0.58)
Left Gray 150	0.562 (–229 – 125)	0.041 (0.03 – 1.57)
Left Gray All	0.428 (–214 – 92)	0.594 (–0.30 – 0.51)
Left White 060	0.104 (–227 – 22)	0.427 (–0.80 – 1.87)
Left White 120	<i>0.074 (–232 – 11)</i>	0.013 (0.29 – 2.36)
Left White All	<i>0.083 (–228 – 14)</i>	0.043 (0.03 – 1.82)
Right Gray 030	0.457 (–215 – 98)	0.891 (–0.50 – 0.57)
Right Gray 060	0.128 (–284 – 36)	0.959 (–0.65 – 0.62)
Right Gray 090	0.314 (–231 – 75)	0.190 (–0.22 – 1.07)
Right Gray 120	0.165 (–253 – 44)	0.175 (–0.20 – 1.08)
Right Gray 150	0.376 (–224 – 86)	0.005 (0.29 – 1.53)
Right Gray All	0.253 (–237 – 63)	0.012 (0.08 – 0.64)
Right White 060	<i>0.075 (–233 – 12)</i>	0.010 (0.39 – 2.68)
Right White 120	0.027 (–267 to –17)	0.002 (0.61 – 2.55)
Right White All	0.037 (–244 to –8)	< 0.001 (0.84 – 2.27)

Note: Data are expressed as *P* value (95% *CI*). Statistically significant ($P < 0.05$; in bold) and near-significant ($P < 0.10$; in italics) differences in SPECT MCP (decreased MCP) and CV (increased CV) between veterans pre-HBOT and Controls (*P* values with 95% confidence intervals) are in shaded cells. Decreased MCP and increased CV are worse blood flow and texture values compared to controls. ROI numbers are in degrees clockwise (left hemisphere) or counterclockwise (right hemisphere) from 12:00 on a clock face of a transverse slice through the centrum semiovale.

DISCUSSION

Forty HBOTs at 152 kPa/60 minutes on a twice/day, 5 days/week schedule is feasible and safe with no long-lasting significant adverse events. Of the three significant events related to the HBOT only increased headache has been reported in mTBI/PPCS/HBOT studies.^{27,30,56} The other two significant adverse events, exacerbation of anxiety, were not collected in a previous report of low-pressure oxygen toxicity effects,¹⁴ reported in other studies of HBOT in PPCS and PPCS/PTSD using similar or greater doses of HBOT on a once/day schedule,^{13,26,28-32} nor reported in other studies of HBOT-induced side effects.⁶ We suspect they were due to the intense twice a day dosing schedule, as was reversible MEBT (16% of subjects), which occurred during the prodrome and early clinical phase of upper respiratory infections and was likely due to the immunosuppressive effects of HBOT.⁵⁷ Twice a day dosing may also explain the bronchospasm/reduction in peak flow in one subject and increased anxiety in two PTSD subjects. Pulmonary oxygen toxicity with decrease in small airways conductance⁵⁸ is typically only seen with higher pressures or prolonged continuous exposures.

The transient symptomatic deterioration at approximately 20 HBOTs is a phenomenon observed in our treatment of other chronic neurological patients that has been incorporated into consent forms. This did not require intervention or discontinuance of treatment. Simultaneously, many

**Table 6: Changes in veterans' brain blood flow and texture of brain blood flow after 1 and 40 HBOTs**

Region of interest	Mean counts/pixel (MCP)		Coefficient of variation (CV)	
	Pre-to-Post-1	Pre-to-Post-40	Pre-to-Post-1	Pre-to-Post-40
Left Gray 030	0.450 (-78 - 171)	0.667 (-209 - 136)	0.050 (-1.30 - 0.00)	0.198 (-0.99 - 0.22)
Left Gray 060	0.531 (-93 - 176)	0.756 (-216 - 159)	<i>0.080 (-1.15 - 0.07)</i>	0.005 (-1.16 to -0.22)
Left Gray 090	0.282 (-60 - 200)	1.000 (-185 - 185)	0.225 (-1.19 - 0.29)	0.779 (-0.76 - 0.57)
Left Gray 120	0.218 (-50 - 210)	0.749 (-201 - 146)	0.107 (-0.97 - 0.10)	0.491 (-1.08 - 0.53)
Left Gray 150	0.396 (-85 - 209)	0.966 (-196 - 188)	0.024 (-1.46 to -0.11)	0.265 (-1.31 - 0.37)
Left Gray All	0.346 (-68 - 188)	0.826 (-198 - 160)	0.005 (-0.96 to -0.19)	0.039 (-0.74 to -0.02)
Left White 060	0.002 (61 - 243)	0.553 (-92 - 169)	0.526 (-1.79 - 0.93)	0.303 (-1.58 - 0.51)
Left White 120	0.002 (52 - 209)	0.784 (-104 - 137)	0.100 (-1.96 - 0.18)	0.046 (-2.11 to -0.02)
Left White All	0.001 (59 - 223)	0.656 (-97 - 151)	0.130 (-1.52 - 0.20)	<i>0.064 (-1.65 - 0.05)</i>
Right Gray 030	0.591 (-89 - 154)	0.622 (-219 - 133)	0.245 (-0.87 - 0.23)	0.333 (-0.86 - 0.30)
Right Gray 060	0.361 (-69 - 183)	0.725 (-206 - 145)	<i>0.055 (-0.89 - 0.01)</i>	0.114 (-0.91 - 0.10)
Right Gray 090	0.318 (-59 - 177)	0.969 (-184 - 177)	0.370 (-0.99 - 0.38)	0.736 (-0.42 - 0.59)
Right Gray 120	0.153 (-31 - 188)	0.906 (-163 - 183)	0.204 (-1.18 - 0.26)	0.851 (-0.75 - 0.62)
Right Gray 150	0.608 (-108 - 181)	0.898 (-185 - 209)	0.415 (-0.71 - 0.30)	0.217 (-0.83 - 0.20)
Right Gray All	0.372 (-66 - 171)	0.901 (-189 - 167)	0.033 (-0.66 to -0.03)	<i>0.087 (-0.42 - 0.03)</i>
Right White 060	0.005 (34 - 174)	0.966 (-121 - 126)	0.127 (-2.28 - 0.30)	0.037 (-2.30 to -0.08)
Right White 120	0.004 (45 - 209)	0.726 (-99 - 141)	0.027 (-1.59 to -0.10)	0.413 (-1.46 - 0.62)
Right White All	0.003 (43 - 189)	0.842 (-107 - 130)	0.024 (-1.71 to -0.13)	<i>0.070 (-1.68 - 0.07)</i>

Note: Data are expressed as P value (95% CI). Statistically significant ($P < 0.05$; in bold) and near significant ($P < 0.10$; in italics) changes in veterans' SPECT MCP and CV pre-HBOT to post-1 and post-40 HBOTs (P values with 95% CI) are in shaded cells. Significant P values indicate improvement after HBOT: more blood flow (MCP) or less heterogeneity (CV). HBOT: Hyperbaric oxygen therapy; CI : confidence interval.

other patients reported an improvement in symptoms at this point, also documented in Wolf et al.¹³ [Figure 2, IMPACT scores at Exposure Interval 5 (20 treatments)]. We speculate that this mid-point in the protocol represents a transition in brain wound adaptation/transformation to the repetitive effects of intermittent hyperoxia and pressure since it corresponds to the time (25 treatments) at which physical changes/improvements were noted in HBOT-treated rats on the same protocol⁵⁹ and the plateau for the angiogenic phase in HBOT-treated human osteoradionecrosis.⁶⁰

Effectiveness of HBOT for blast TBI and PTSD

The major findings in this study were: 1) the significant improvements and magnitude of improvements in all outcome instruments (symptoms, cognition, mood, quality of life, and imaging) that were reproducible (strengthened P values) from the first 16 subjects²⁷ to the final 14 subjects, 2) the abnormal brain blood flow pattern that became nearly indistinguishable from Controls after treatment, 3) one of the longest follow-up periods of any HBOT/PPCS study, 4) the increased symptom improvement six months post treatment, and 5) the reduction in suicidal ideation. Effect sizes and confidence intervals were substantial. These findings were mirrored by a reciprocal reduction or elimination of psychoactive and narcotic prescription medication usage, and maintained abstinence from the same medication discontinued immediately pre-HBOT.

Headache is a known marker of TBI PPCS and distinguishes TBI PPCS from PTSD in blast brain-injured U.S. soldiers.³ The significant reduction in headaches suggests treatment of TBI and the organic injury of TBI established by our subjects' loss of consciousness.^{61,62} It also is consistent with and reaffirms the previous animal work on HBOT in chronic TBI wounding⁵⁹ at a similar dose of HBOT (152 kPa/90 minutes twice/day, 7 days/week). These findings are similar to the findings in the previously mentioned human experience with moderate to severe chronic TBI,¹⁵⁻²³ and blast-induced mTBI uncomplicated by PTSD.²⁶ Collectively, they suggest treatment of cerebral wounds from TBI.

The PTSD symptom reduction is one of the greatest reductions in PTSD symptoms in a four-week period with any reported treatment⁶³ and combined with the effect on PPCS outcomes represents the only reported treatment for the combined diagnoses of blast-induced PPCS and PTSD. The 18.8-point reduction in PCL-M is greater than the PCL-M reduction in 13/16 RCTs of second-line interventions in military-related PTSD.⁶⁴ Half of the subjects no longer met the PCL-M threshold criteria for diagnosis of PTSD. A lesser reduction of PTSD symptoms has been confirmed in all three DoD-funded HBOT studies.^{13,29,30} Spontaneous recovery of PPCS or PTSD 3.35 years after injury and further improvement in PPCS symptoms 6 months post-treatment is contrary to the natural history of TBI, PTSD, and TBI with PTSD in veterans.⁶⁵ Coupled with the significant



Table 7: Comparison of veterans' brain blood flow and texture of brain blood flow to Controls before, after 1, and after 40 HBOTs.

Region of interest	Mean counts/pixel (MCP)			Coefficient of variation (CV)		
	Pre	Post 1	Post 40	Pre	Post 1	Post 40
Left Gray 030	0.374 (-218 - 83)	0.775 (-165 - 124)	0.175 (-256 - 48)	0.647 (-0.52 - 0.83)	<i>(+) 0.086</i> <i>(-1.06 - 0.07)</i>	0.445 (-0.85 - 0.38)
Left Gray 060	0.251 (-248 - 66)	0.491 (-192 - 93)	0.134 (-277 - 38)	0.708 (-0.54 - 0.79)	0.223 (-1.10 - 0.26)	<i>(+) 0.070</i> <i>(-1.18 - 0.05)</i>
Left Gray 090	0.640 (-188 - 116)	0.629 (-107 - 176)	0.658 (-196 - 125)	0.310 (-1.32 - 0.43)	(+) 0.025 (-1.68 to -0.12)	0.176 (-1.33 - 0.25)
Left Gray 120	0.441 (-214 - 95)	0.785 (-127 - 167)	0.273 (-245 - 71)	0.783 (-0.76 - 0.58)	0.139 (-1.24 - 0.18)	0.347 (-1.14 - 0.41)
Left Gray 150	0.562 (-229 - 125)	0.890 (-140 - 161)	0.510 (-224 - 112)	(-) 0.041 (0.03 - 1.57)	0.966 <i>(-0.64 - 0.67)</i>	0.428 <i>(-0.50 - 1.17)</i>
Left Gray All	0.428 (-214 - 92)	0.988 (-141 - 139)	0.304 (-236 - 75)	0.594 (-0.30 - 0.51)	(+) 0.034 (-0.89 to -0.04)	0.183 (-0.68 - 0.13)
Left White 060	0.104 (-227 - 22)	0.410 (-70 - 168)	0.336 (-198 - 69)	0.427 (-0.80 - 1.87)	0.864 (-1.14 - 1.35)	0.997 (-1.28 - 1.28)
Left White 120	<i>(-) 0.074</i> <i>(-232 - 11)</i>	<i>0.715</i> <i>(-90 - 130)</i>	<i>0.147</i> <i>(-223 - 34)</i>	(-) 0.013 (0.29 - 2.36)	<i>0.348</i> <i>(-0.48 - 1.35)</i>	<i>0.638</i> <i>(-0.83 - 1.35)</i>
Left White All	<i>(-) 0.083</i> <i>(-228 - 14)</i>	<i>0.534</i> <i>(-76 - 146)</i>	<i>0.219</i> <i>(-207 - 48)</i>	(-) 0.043 (0.03 - 1.82)	<i>0.477</i> <i>(-0.48 - 1.02)</i>	<i>0.773</i> <i>(-0.76 - 1.01)</i>
Right Gray 030	0.457 (-215 - 98)	0.724 (-175 - 122)	0.219 (-265 - 62)	0.891 (-0.50 - 0.57)	0.291 (-0.81 - 0.25)	0.370 (-0.77 - 0.29)
Right Gray 060	0.128 (-284 - 36)	0.360 (-211 - 78)	(-) 0.064 (-317 - 9)	0.959 (-0.65 - 0.62)	0.149 (-1.08 - 0.17)	0.174 (-1.03 - 0.19)
Right Gray 090	0.314 (-231 - 75)	0.783 (-157 - 119)	0.331 (-247 - 85)	0.190 (-0.22 - 1.07)	0.718 (-0.55 - 0.79)	0.121 (-0.14 - 1.16)
Right Gray 120	0.165 (-253 - 44)	0.724 (-169 - 118)	0.268 (-263 - 75)	0.175 (-0.20 - 1.08)	0.958 (-0.69 - 0.66)	0.186 (-0.19 - 0.94)
Right Gray 150	0.376 (-224 - 86)	0.666 (-182 - 117)	0.508 (-227 - 114)	(-) 0.005 (0.29 - 1.53)	(-) 0.020 (0.12 - 1.29)	(-) 0.047 (0.01 - 1.18)
Right Gray All	0.253 (-237 - 63)	0.628 (-174 - 106)	0.234 (-260 - 65)	(-) 0.012 (0.08 - 0.64)	0.928 <i>(-0.31 - 0.34)</i>	0.245 <i>(-0.12 - 0.44)</i>
Right White 060	<i>(-) 0.075</i> <i>(-233 - 12)</i>	<i>0.917</i> <i>(-126 - 113)</i>	<i>0.100</i> <i>(-237 - 21)</i>	(-) 0.010 (0.39 - 2.68)	0.407 <i>(-0.76 - 1.84)</i>	0.557 <i>(-0.83 - 1.52)</i>
Right White 120	(-) 0.027 (-267 to -17)	<i>0.799</i> <i>(-126 - 98)</i>	<i>(-) 0.067</i> <i>(-250 - 9)</i>	(-) 0.002 (0.61 - 2.55)	0.114 <i>(-0.18 - 1.64)</i>	(-) 0.030 (0.11 - 2.20)
Right White All	(-) 0.037 (-244 to -8)	<i>0.854</i> <i>(-122 - 101)</i>	<i>(-) 0.074</i> <i>(-240 - 12)</i>	(-) <0.001 (0.84 - 2.27)	0.109 <i>(-0.15 - 1.42)</i>	<i>(-) 0.086</i> <i>(-0.11 - 1.61)</i>

Note: Data are expressed as *P* value (95% *CI*). Statistically significant ($P < 0.05$; in bold) and near-significant ($P < 0.10$; in italics) differences in SPECT MCP and CV between veterans pre-HBOT, post-1 HBOT, and post-40 HBOTs and Controls (*P* values) with 95% *CI* are in dark shaded cells. Negative *P* values for MCP indicate decreased MCP (worse) compared to Controls at each time point. Negative *P* values for CV indicate increased CV (worse) and positive *P* values for CV indicate decreased CV (better) compared to Controls at each time point. Diagonal lined cells indicate improvements in abnormal pre-HBOT MCP and CV values after 1 and 40 HBOTs. The black box is the sole deterioration after HBOT. HBOT: Hyperbaric oxygen therapy; *CI*: confidence interval.

cognitive improvements demonstrated by Reliable Change Score analysis these outcomes argue for cause and effect of HBOT in PPCS and PTSD.

The magnitude of these cognitive and affective improvements was criticized based on historically minimal or absent decreases in intellectual function after simple mild TBI.^{66,67} This magnitude of improvement is likely due in part to treatment of both TBI and PTSD,^{63,68,69} treatment of patients with multiple TBIs,⁷⁰ treatment of combined blast and blunt TBI, use of the broad 25th-75th percentile range as “normal,” and reporting of an infrequent measure of concussion damage,

full scale IQ. It also suggests a bias in neuropsychological testing of patients in which the definition of “normal” or “average” intellectual ability is construed to mean no damage or deficit. Our subjects complained of a reduction in their basic intellectual abilities and that they were not back to their “normal” cognitive levels, yet their FSIQ and VWM were “normal” and “average” before treatment. According to the patients, their complaints were often dismissed or attributed to emotional factors or even malingering. After treatment their FSIQ, memory, and other cognitive scores improved significantly to above “normal”/average levels,

**Table 8: Summary of Department of Defense-funded and civilian studies on HBOT in mild TBI/PPCS.**

Author	Type	N	Dose (kPa)	Outcome imaging	Outcome PPCS	Outcome PTSD	Outcome PTSD/PPCS
Harch et al. ²⁵	Case Report	1	152 O ₂	+	+	+	+
Wright et al. ²⁶	Case Report	2	152 O ₂		+		
Harch et al. ²⁷	Prospective Case Series	30	152 O ₂	+	+	+	+
Wolf et al. ¹³	RCT	50	132/122 air vs. 243 O ₂		+	+	
Boussi-Gross et al. ²⁸	RCT	71	No pressure	0	0		
			152 O ₂	+	+		
			Crossover	+	+		
Scorza et al. ¹² (subset Wolf et al. ¹³)	RCT	50	132/122 air vs. 243 O ₂		?	+	+
					+	+	
Cifu et al. ²⁹	RCT	60	203P/21 O ₂	0	0	0	
			203P/152 O ₂	0	0		
			203P/203 O ₂	0	+		
Walker et al. ³¹	RCT	60	203P/21 O ₂	? 0 ⁺			
			203P/152 O ₂	? 0 ⁺			
			203P/203 O ₂	? 0 ⁺			
Cifu et al. ³²	RCT	60	203P/21 O ₂	? 0 [#]			
			203P/152 O ₂	? 0 [#]			
			203P/203 O ₂	? 0 [#]			
Miller et al. ³⁰	RCT	72	No pressure	0		0	
			122 air	+	+		
			152 O ₂	+	+		

Note: "*" No within group pre/post testing; "#" No within group pre/post testing, yet multiple significant cognitive outcomes reported for the entire cohort in Additional files of the study. "?" Not mentioned in abstract. Blue shading represents positive, gray represents neutral or indeterminate, red represents negative study outcomes at a given dose of HBOT. HBOT: Hyperbaric oxygen therapy; TBI: traumatic brain injury; PPCS: persistent post-concussion syndrome; PTSD: post-traumatic stress disorder.

underscoring that they were not "normal"/average or at their previous normal level after their concussion(s). The treatment results were independent of effort (Green Word Memory Test) and greater than would be expected by test-retest/practice effects (Reliable Change Score analysis). Accepting "Average" as a post-injury assessment of "normal" can lead to inaccurate judgments and suggests that general intellectual ability and memory outcome instruments should be more commonly employed in PPCS treatment studies.

Subjects experienced large emotional improvements. 83% of subjects with suicidal ideation and 75% of subjects with panic attacks experienced a reduction or cessation in suicidal ideation or panic attacks after treatment. This is the first report of reduction in suicidal ideation or panic attacks in a hyperbaric therapy study on veterans. Self-reported Quality of Life and the subjects' estimate of the percent of their pre-deployment "normal" level of function also improved significantly. The reductions in suicidal ideation, panic attacks, and psychoactive medication use have implications for the current suicide epidemic in veterans. This is particularly meaningful, considering the contribution of psychoactive medication to veteran suicides.⁷¹

All of the veterans' non-imaging deficits, and improvements after HBOT, were explained by the brain blood flow

findings. The main blood flow abnormalities, lower blood flow and coarse texture, were found in the white matter consistent with the primary injury site in mTBI.^{72,73} These abnormalities were statistically normalized or near normalized after HBOT. The improved texture corresponds to the pattern of blood flow seen in normal people (**Figure 3**) and HBOT-treated patients with a variety of chronic neuropathologies (trauma, carbon monoxide poisoning, decompression sickness, near-drowning, cerebral palsy)^{17,18,74,75} in the past two decades and is consistent with the findings reported with perfusion CT using our protocol of HBOT 152 kPa on chronic severe TBI, anoxic, and stroke patients.⁷⁶ Taken together, the overall unchanged blood flow (MCP) and decreased range of blood flow (improved CV) after 40 HBOTs suggests that HBOT normalized brain blood flow by simultaneously decreasing elevated brain blood flow and increasing lowered brain blood flow.

The unchanged total amount of brain blood flow after 40 treatments is different from the findings in the first 16 subjects of this study reported with statistical parametric mapping²⁷ and other SPECT HBOT chronic TBI studies^{19,28} which noted increased brain blood flow after a course of HBOT. These discrepancies are likely due to differences in analytic methodologies and the heterogeneity of the

**Table 9: Oxygen and pressure dose relationship of studies in Table 8**

kPa	122	132	142	152	162	172	182	193	203	213	223	233	243
21									-PPCS [±]				
28		+PPCS* +PTSD*							-PTSD [±]				
41													
51													
61													
71													
81													
91													
101													
111													
122													
132													
142													
152				+PPCS [±] +PTSD [±]					-PPCS [±] -PTSD [±]				
162													
172													
182													
193													
203									-PPCS [±] +PTSD [±]				
213													
223													
233													
243													-PPCS [§] +PTSD [§]

Note: *Reference 13, 30; +References 25-28, 30, for PPCS. Reference 25, 27, 30 for PTSD. ±Reference 29. §Reference 12 for PPCS. Reference 12 and 13 for PTSD. Total pressure in kilo Pascals (kPa) is in columns and oxygen pressure in rows. “+” and “-” denote positive and (unchanged or negative) study outcomes, respectively, in either PPCS or PTSD. Light gray shading is drawn at and below the total and oxygen pressure limit lines for all positive outcomes and black shading at and above the total and oxygen pressure limit line for negative outcomes. All blank gray, white, and black shaded areas represent untested doses. All positive outcomes for PPCS are < 203 kPa and all positive outcomes for PTSD are at equal total and oxygen pressures or a low level of hyperoxia compared to increased pressure.

samples/injuries. The common finding is HBOT-induced improvement in either amount or pattern of brain blood flow. Based on flow-metabolism-function coupling⁷⁷⁻⁸⁰ these improvements in blood flow are physiologically responsible for the improvements in symptoms, physical exam, cognition, emotional state, and quality of life experienced by our subjects. Collectively, the SPECT/HBOT/TBI literature^{15-23,28} suggests the utility of SPECT in TBI⁸¹ and as a surrogate endpoint in mTBI/PPCS.⁸²

The different effects of one and 40 HBOTs on brain blood flow (Table 6) reaffirmed the findings on the first 16 subjects,²⁷ suggesting different metabolic/physiology effects of a single vs. 40 consecutive HBOTs in chronically injured brain. These effects are inconsistent with placebo effects documented with SPECT.^{83,84} In addition, the symptom and cognitive improvements in subjects occurred progressively

and were apparent at 40 HBOTs, similar to Wolf et al.,¹³ not after the first HBOT, underscoring that the cognitive and symptom improvements were related to the brain blood flow normalization after 40 HBOTs. This is consistent with the SPECT and cognitive improvements after 40 treatments in Boussi-Gross et al.²⁸ and the cognitive improvements after more than 35 treatments in Golden and Neubauer et al.²⁰

HBOT is a treatment for acute, subacute, or chronic wounds in any anatomical location.^{5,6} In the preliminary report²⁷ it was argued that HBOT was treating the microscopic white matter wounds of TBI. Recent reports in animals and humans have proven the existence of primarily perivascular white matter wounds in chronic blast-induced TBI,^{85,86} which are similar in location to the perivascular white matter wounds of chronic cerebral decompression sickness,⁸⁷ the original wound to which we applied HBOT

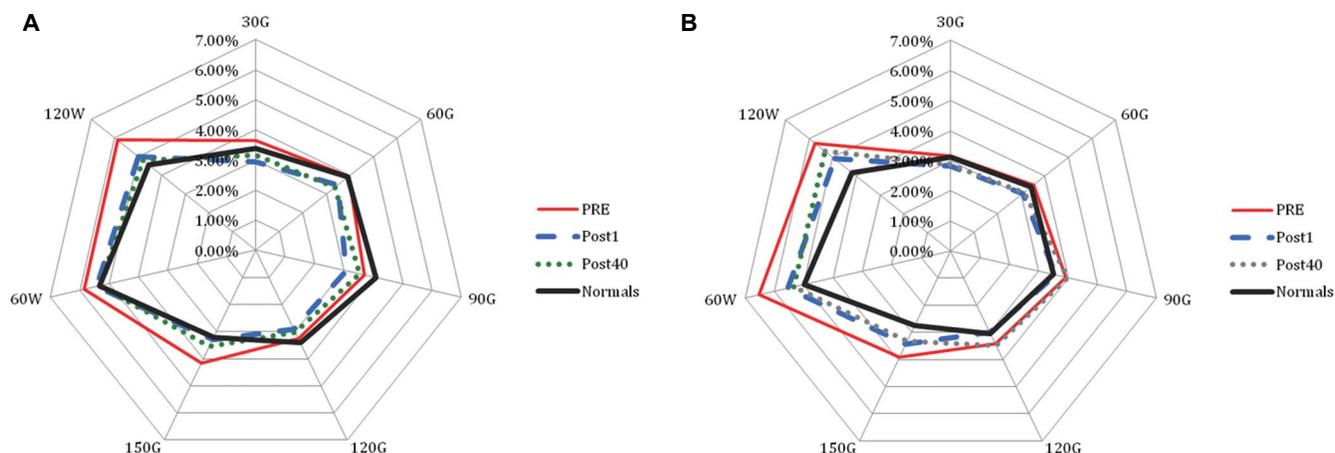


Figure 2: Radar graph of left (A) and right (B) hemisphere.

Note: Average CV for each ROI of Controls (Normals) vs. Veterans (Pre, Post 1, and Post 40 HBOTs). Error bars omitted for viewing clarity. CV: Coefficient of variation; ROI: region of interest.

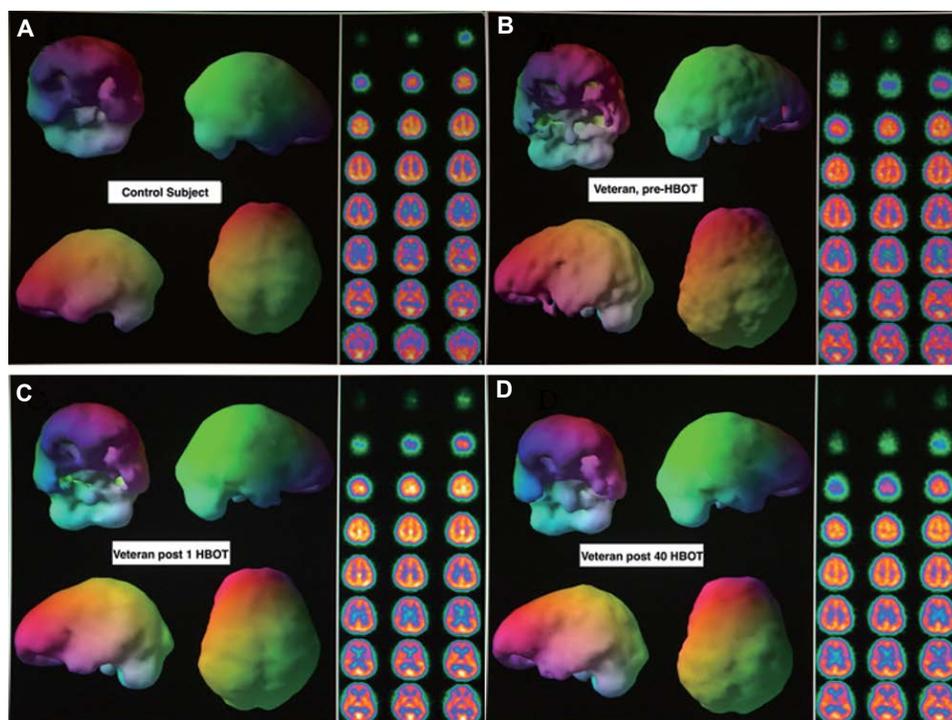


Figure 3: Transverse zoom slices and three-dimensional surface reconstruction of control subject (A) and veteran pre-HBOT (B), after 1 HBOT (C), after 40 HBOTs (D) SPECT brain blood flow scan.

Note: Colors for the slices represent gradations of blood flow from highest to lowest: white, yellow, orange, purple, blue, black. Color scheme in the three-dimensional reconstructions are aesthetic and embedded in the Picker software.

152 kPa in 1990.⁸⁸ The presence of white matter wounds is consistent with the reductions in white matter blood flow in the present study. The global symptomatic, cognitive, affective, physical exam, and imaging improvements in our studies and the studies of others^{13,16,19,20,26,28,30-32,76} are consistent with the known wound-healing effects of HBOT on the diffuse cerebral microscopic wounds of TBI.

The microscopic wound model, however, does not explain the surprising improvement of PTSD symptoms in the subjects. Persistence of PTSD has demonstrated long-term evidence of brain wounding,⁸⁹ yet no pathological⁹⁰ or imaging⁷⁰ signature is evident. PTSD shares some of the same anatomical areas involved with TBI/PPCS.^{89,91-93}

We speculate that in the course of treating the TBI/PPCS wounds the pathways for recurring pathological thoughts of PTSD are interrupted similar to interruption of cardiac re-entrant rhythms with medication or ablation therapies. This speculation is supported by the successful treatment of PTSD with stellate ganglion block.⁹⁴ The mechanism of action is possibly modulation of gene expression. A recent study reveals genetic influences on the development of PTSD and shared genetic risk between PTSD and schizophrenia, bipolar, and major depressive disorder.⁹⁵ HBOT may be suppressing these genes in a similar fashion to *in vitro* studies.⁹⁶⁻⁹⁹

The significant outcomes in this study demand interpre-



tation in the context of the subsequent more rigorous,^{28,30} and multi-dosing studies^{13,29} and their confusing results/conclusions.^{13,29-32,100-102} Since the first application of HBOT 152 kPa to Veterans with mTBI/PPCS and PTSD²⁵ other researchers have: 1) duplicated HBOT-induced mTBI/PPCS improvements with the same HBOT 152 kPa dose using a stronger experimental design,^{29,31} 2) demonstrated positive^{13,30} and negative (“harmful”)¹² effects with different doses of HBOT (243 kPa oxygen, 122 kPa and 132 kPa air), and 3) demonstrated neutral²⁹ or indeterminate^{31,32} effects with three alternate doses (203 kPa pressure/21 kPa oxygen, 152 kPa oxygen, or 203 kPa oxygen). HBOT PTSD studies have shown benefit at 152 kPa oxygen,^{25,27,30} 203 kPa oxygen,²⁹ 243 kPa oxygen,¹³ 132/122 kPa air,^{13,30} and no benefit at 203 kPa pressure/(21 kPa oxygen or 152 kPa oxygen).²⁹ The two recent studies by Wolf and colleagues^{100,101} preclude comparative dosing analysis due to lack of actual data; both publications featured derived data/statistics. All of these studies except the recent Wolf’s studies^{100,101} are summarized in **Table 8**. Since HBOT is a combination therapy of increased pressure and increased oxygen^{4,5} the discrepancies in experimental results for all studies and diagnoses are best explained by the effects of different doses of hyperbaric therapy on different neuropathologies, multi-dose study designs, mis-definitions of HBOT and sham, confusing statistical analyses, and erroneous conclusions.^{4,5,102-104} A dose-response relationship with both oxygen and pressure is strongly suggested by **Table 9**. The oxygen component of this dose argument has been supported by others.¹⁰⁴ The data^{12,13,25-32} suggest that the pure 152 kPa dose of oxygen and the 132/122 kPa air pressurization doses are beneficial in PPCS with or without PTSD (**Table 8**) and that the 152 kPa oxygen dose has durability (present study with 6-month phone follow-up).

Alternative explanations posited for our data and the data of the DoD-funded studies^{13,29-32} are placebo, relocation, Hawthorne, test/retest and practice effects, and the “ritual of HBOT”,³⁰ collectively referred to as Non-Treatment Effects. All of these Non-Treatment Effects, except relocation and ritual, were previously addressed in multiple publications.^{27,63,68} They cannot explain the multiplicity of positive findings across all domains in our study, especially the imaging findings,^{27,63,68} and are refuted by the disparity in reported data from all of the mTBI studies reviewed above.^{12,13,25-32} Placebo and relocation effects should be greatest in beautiful Pensacola, Florida, but this study site had the least positive or neutral effects.^{29,31,32} The bulk of improvements accrued in the first 20 treatments in Miller et al.,³⁰ were absent in the 203 kPa pressure studies,^{29,31,32} occurred after 20 treatments in the Wolf et al.’s¹³ air group, and were present in the first 20 treatments, lost in the second 20 treatments, and regained in the post-treatment period in Wolf et al.’s¹³ HBOT group.

These disparities are not consistent with placebo effects where more placebo would be expected to have increasing and sustained effects. In addition, durability of placebo effects¹⁰⁵ and further improvement after placebo treatment are uncommon. Rather, they are consistent with the 3 patterns of improvement identified in a review of placebo-drug studies that differentiate true drug effects of different doses of HBOT from the 61 placebo effect patterns.¹⁰⁶

A more recent explanation, the “ritual” of the hyperbaric chamber experience³⁰ is a theoretical contribution to placebo effect and is likely a component of the placebo effect, but it was argued based on the mischaracterization of sham in previous articles. It is inconsistent with the varied results in the DoD studies above. All of these studies contained the same “ritual” experience as the present study and should have had the same positive results. They did not. In addition, ritual does not explain the improvement of cognition and blood vessel density in an animal model of mTBI⁵⁹ that used the original human protocol of 152 kPa oxygen, a near identical dose of hyperbaric therapy to the present study.

The more likely alternative to the multiple non-treatment and placebo effects explanations is the one that is consistent with the data, the biology of hyperbaric therapy,⁶ and Occam’s razor¹⁰⁷ HBOT is a known therapy for wounds whose effects are dependent on dose. Mild TBI/PPCS is characterized by persistent white matter microscopic wounds.^{85,86} HBOT in this study is treating the microscopic white matter wounds of chronic TBI and the associated psychiatric condition of PTSD that invests these wounds. The differences in results between clinical studies are due to differences in doses of hyperbaric therapy.

A single dose of HBOT can induce excitability and neural plasticity of hippocampal neurons in normal rat brain slices¹⁰⁸ while repetitive doses in an injury model have shown neurogenesis.¹⁰⁹ The mechanism of action of HBOT in central nervous system (CNS) wounds are unknown but likely similar to those in non-CNS wounds.⁶ HBOT exerts its wound-healing effects by expression and suppression of oxygen and pressure sensitive genes.⁹⁶ A single HBOT to human microvascular endothelial cells upregulated and downregulated 8,101 genes in 24 hours and enhanced vascular network formation. The primary gene clusters affected were the anti-inflammatory genes and genes that code for cell growth and proliferation. These gene-activating effects and tissue responsiveness are dependent on the dose of hyperbaric oxygen and pressure applied.^{4,97-99} The improvements, neutral, or negative effects of hyperbaric therapy in the multiple studies^{13,25-32} reflect the doses of pressure and hyperoxia that were applied to chronic brain wounds in the various studies. Some doses are effective, some are ineffective, and one is harmful in the treatment



of PPCS, PTSD, and PPCS with PTSD. Repair of chronic brain wounds by trophism is supported by the durability of the clinical improvements in our subjects. At 6-month follow-up all subjects not only maintained improvement, but also reported further improvement.

Historical protocols have demonstrated that 30–40 HBOTs are necessary for healing of chronic non-CNS wounds,⁶ similar to the number of treatments in our study, however, it is half the number of HBOTs (80) that we have used clinically in more severe cases.^{15–23} In our original animal pilot study we compared 40 and 80 HBOTs to 40 sham air treatments and found a greater effect on memory and blood vessel density with 80 HBOTs vs. 40 HBOTs.¹¹⁰ This became the final protocol of the animal model.⁵⁹ The animal studies and previous clinical experience with chronic moderate to severe TBI^{15–23,76} suggests our subjects might show further improvement with additional HBOT as was shown in Wright et al.'s use of the 152 kPa protocol.²⁶

The limitations of the present study were unblinded investigators, and lack of a treatment control group. Placebo/non-treatment effects were discussed above. Investigator bias likely contributed to the magnitude of some of the P.I.'s symptom and physical exam recording and author SRA's neuropsychological testing, but are unlikely to account for the majority of the effects or the consistency and magnitude of the effects across all domains. This is particularly true for the SPECT subject/SPECT Control Group analyses where the investigators did not interact with the subjects and performed their analyses months to years after the subjects had completed their final imaging. Lack of a treatment control group is addressed with the placebo discussion and the results of the treatment-controlled studies. Currently, we are conducting a randomized controlled study of HBOT 152 kPa in civilians and military subjects with mTBI PPCS without clinical PTSD.

In conclusion, a 30-day course of 40 HBOT treatments delivered at 152 kPa/60 minutes, twice/day, 5 days/week, to military subjects with PPCS of mild-moderate blast-induced TBI with or without PTSD was safe with no persistent adverse events. Acute adverse events were more common than in other studies and the investigator's historical experience, but were felt to be due to the intense dosing schedule. Subjects experienced significant improvements in PPCS and PTSD symptoms, physical exam abnormalities, cognition, depression, anxiety, quality of life, and brain blood flow that cannot be explained with non-treatment effects; they are more consistent with the known wound-healing effects of HBOT on the diffuse cerebral microscopic wounds of TBI. Moreover, symptomatic improvements increased further during the 6-month post-treatment period. Compared to the

matched Controls, TBI/PTSD subjects' brain blood flow was abnormal, but became visually more normal and statistically near-indistinguishable from Controls after 1 and 40 HBOTs. The main blood flow abnormalities and changes in blood flow after HBOT were in the white matter, the primary site of injury in mTBI. Simultaneously and most importantly, subjects experienced a significant reduction in suicidal ideation and anxiety, possibly the most significant finding in the study given the current veteran suicide epidemic. At the same time they were able to discontinue or decrease the dosage of their psychoactive medications and 52% no longer met the criteria for PTSD. These data comprise the strongest evidence and only treatment to date for the combined diagnoses of blast-induced PPCS with PTSD, and thus represent the best evidence-based medicine¹¹¹ for these dual-diagnoses.⁶⁸

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Author contributions

PGH, SRA, EFF, JL, KWVM: Contributions to the conception or design of the work; PGH, SRA, EFF: interpretation of data; PGH, SRA, EFF, JL, KWVM: contributions to the acquisition and analysis of data for the work, and drafting the article; PGH, SRA, EFF: manuscript edition; PGH, SRA, EFF, JL, KWVM: final approval of the article.

Conflicts of interest

Dr. Harch owns a small hyperbaric medicine consulting company. He derives income from the treatment facility that is the primary location of his medical practice. He is on the board of directors of the International Hyperbaric Medical Association, a non-profit professional organization, and derives no income from this organization. Dr. Fogarty is president of the International Hyperbaric Medical Foundation (IHMF), a non-profit corporation that promotes education, research, and teaching in hyperbaric medicine. He also owns a holding company for a mobile hyperbaric clinic. Dr. Andrews has no competing financial interests. Juliette Lucarini, is co-owner of the hyperbaric consulting company with Paul G. Harch, M.D. Dr. Van Meter owns a hyperbaric equipment leasing company and contracts with hospitals to provide hyperbaric medicine physician staffing. Dr. Van Meter also owns the treatment facility. Partial presentation of a small subset of data at HBOT 2014 (The 9th International Symposium on Hyperbaric Oxygenation: Roadmap for the Future). Presented two slides on *P* values for the cognitive



and quality of life outcomes for the first 24 subjects, compared to the first 15 subjects, in a lecture on review of the science and literature of HBOT in persistent post-concussion syndrome. None of the imaging, demographics, and content of the tables in this manuscript were presented at that meeting.

Research ethics

The study protocol was approved by the Louisiana State University Institutional Review Board. The study followed international and national regulations in accordance with the *Declaration of Helsinki*. The trial was registered with ClinicalTrials.gov (identifier: NCT00760734).

Data sharing statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Plagiarism check

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Open peer reviewers

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Additional files

Additional Table 1: List and Schedule of Psychometric Measures, When Administered, and Domain Measured.

Additional file 1: Re-Analysis of All Variables by Green Pass/Fail.

Additional file 2: Association of Improvements in Sleep and Medication with Changes in NeuroPsych and SPECT Variables.

Additional file 3: Contribution of Moderate TBI to Composite Data.

Additional file 4: Analysis of SPECT Data.

Additional file 5: Approach of SPECT MCP and CV at baseline, post-1 HBOT, and post-40 HBOTs to Control Subjects' MCP and CV.

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