WESTERN IRB PROTOCOL

National Brain Injury Rescue and Rehabilitation Study (NBIRR)

A Multicenter Observational Study of Hyperbaric Oxygen Therapy (HBOT) in Chronic Traumatic Brain Injury (TBI)/Post-Concussion Syndrome (PCS) and TBI/Post-Traumatic Stress Disorder (PTSD)

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SPONSOR:
International Hyperbaric Medical Foundation (IHMF)
Paul G. Harch, MD, President
8210 Cinder Bed Road Ste C-3
Lorton, Virginia 22079-1135
Telephone: (703) 339-0900 FAX: (703) 952-0244

MEDICAL MONITOR:
to be determined

PRINCIPAL INVESTIGATORS on BEHALF OF SPONSOR:

James Wright, MD
Vice President, Research
3400 Hannibal
Butte MT 59701
(850) 855-8582

B. Robert Mozayeni, MD
CareVector, LLC
(240) 678-8618
brmoffice@verizon.net

SUMMARY OF REVISIONS

This protocol is listed in clinicaltrials.gov and has been enrolling patients since May 2010. The revision consists in an updated scientific basis for HBOT's clinical effects.

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GLOSSARY OF TERMS

ANAM	Automated Neuropsychiatric Testing
ANOVA	Analysis of variation
APC	Administrative Project Coordinator
CES	Combat Exposure Scale
CITI	Collaborative Institutional Training Initiative
CNS	Central nervous system
CP	Cerebral palsy
CVP	CareVector Platform™
DCI	Decompression illness
FDA	U.S. Food and Drug Administration
FTT	Finger tapping test
FWA	Federal-wide Assurance
GCP	Good Clinical Practices
HBO	Hyperbaric oxygen
HBOT	Hyperbaric oxygen therapy

HBOT 1.5	Hyperbaric oxygen therapy at 1.5 atmospheres of pressure
IED	Improvised Explosive Device
IRB	Institutional Review Board
LOC	Loss of consciousness
LSUHSC	Louisiana State University Health Sciences Center
MPQOL	Modified Perceived Quality of Life Scale
MVA	Motor vehicle accident
NBIRR	National Brain Injury Rescue and Rehabilitation Study
OHRP	Office for Human Research Protections, U.S. Department of Health and Human Services
PBNRS	'Percent-Back-to-Normal' rating scale
PCL	PTSD Checklist
PCS	Post-concussion syndrome
PHQ	Patient health questionnaire
PTSD	Post-traumatic stress disorder
SAT	Shifting Attention Test
SDC	Symbol Digit Coding
SPECT	Single photon emission computed tomography
SPM	Statistical parametric mapping
TBI	Traumatic brain injury
VBM	Verbal memory test
VIM	Visual memory test
WBC	White blood cell

National Brain Injury Rescue and Rehabilitation Study (NBIRR)

...a Multicenter Study of Hyperbaric Oxygen Therapy (HBOT) at Low Pressure in Chronic Traumatic Brain Injury (TBI)/Post-Concussion Syndrome (PCS) and TBI/Post-Traumatic Stress Disorder (PTSD)

SUMMARY

Purpose

This is an observational study of hyperbaric oxygen therapy (1.5 atmospheres, 100% O2) for traumatic brain injury (TBI) with or without Post Traumatic Stress Disorder (PTSD) to ascertain in a large, multicenter cohort if there is a long term benefit for a new use of a known safe treatment.

Goals

a) Provide access to a safe treatment for a new indication of an FDA-cleared Medical device for mild-moderate chronic TBI and/or PTSD while ascertaining broader efficacy under controlled conditions.
b) Ascertain the optimal number of treatments in the range from 40-80 HBOT sessions.
c) Ascertain long-term (2 year) outcome of the HBOT 1.5 ata protocol.

Specific Aims

In this study we evaluate patients who have debilitating Post-Concussion Syndrome (PCS), and/or PTSD, as they undergo treatment with a course of low-pressure hyperbaric oxygen therapy (HBOT 1.5). We believe HBOT 1.5 treatment has the potential to return patients to work, school, or previous level of function and significantly minimize the personal and societal costs of TBI/PTSD. We propose to study HBOT 1.5 treatment, track the results of the treatment, and track outcome measures for 1,000 patients with TBI or PTSD to find the optimal care pathway for these conditions.

Our primary specific aim is to determine whether 40, 60 or 80 HBOT 1.5 treatments generate significant improvement in cognitive function in mild TBI patients with PCS and/or PTSD. Secondary aims are: 1) determine if automated cognitive function testing and quality of life measures can track this improvement; 2) determine which psychometric test measures, QOL measures, or indices of return to school, work, or previous level of function is the most sensitive outcome to use in subsequent research; and 3) determine how the above measures correlate with specific neurological exam findings.

BACKGROUND

Definition of TBI

Traumatic brain injury (TBI) survivors include patients that span the entire spectrum of TBI and TBI disability: mild, moderate, and severe. TBI is a graded injury with degree of injury, pathological findings, and disability proportional to the magnitude of force impacting the head. Progressively greater force causes greater pathological damage which is composed of elements of injury found in less severe forms of TBI (axonal injury) as well as the pathology specific to more severe levels of injury (parenchymal hemorrhage, extra-parenchymal hemorrhage, etc.). Blast overpressure, without being accompanied by the same physical trauma seen in sports injuries, automobile accidents, etc., is also causing organic injury that manifests in symptoms virtually identical to the blunt force trauma usually associated with TBI. It actually is multiple types of brain trauma. As a result, conclusions drawn about treatment of the pathology and disability of mild TBI should also be applicable to more severe degrees of TBI. Despite different definitions of mild TBI[1], 15-29% of the mild TBI population has appreciable complaints six months after injury. These ongoing symptoms have been termed Post-Concussion Syndrome (PCS), and this syndrome is associated with a high degree of morbidity and unemployment[2]. At one year, the incidence declines slightly to 10-15%, but many of these individuals are at risk for developing persistent PCS, a syndrome of organic and psychiatric pathology.

Both of these syndromes collectively referred to as PCS in this application, have long-term cognitive, social, emotional, and psychological dysfunction that our proposed treatment may address. Since both civilian and military mild TBI patients and mild TBI sequelae patients with PCS comprise the largest, most visible, and controversial of TBI patients this discussion and scientific argument will focus on them, while the study will include both mild and moderate TBI patients.

Epidemiology

TBI is a significant public health problem in the United States, affecting 100/100,000 population. The prevalence of chronic TBI is 2.5-6.5 million, a vast underestimate due to under-diagnosis and reporting bias against mild TBI[3]. The personal, social, and economic toll is staggering. Direct and indirect financial costs alone were estimated at $56 billion/year in 1995[4]. Emotional, social, and personal costs are far higher, yet difficult to estimate. Of greater concern is the fact that there are no widely accepted effective treatment methods for chronic sequelae of TBI, i.e., PCS.[5]

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[1] Bohnen N, Twijnstra A, Jolles J. Persistence of postconcussional symptoms in uncomplicated, mildly head-injured patients: a prospective cohort study. Neuropsychiatry Neuropsychol Behav Neurol, 1993; 6: 193-200.
[2] Rapoport M, McCauley S, Levin H, et al. The Role of Injury Severity in Neurobehavioral Outcome 3 Months After Traumatic Brain Injury. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 2002;15(2): 123-132.
[3] NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. Rehabilitation of Persons With Traumatic Brain injury. JAMA, September 8, 1999; 282 (10): 974-983.
[4] Thurman DJ. Epidemiology and economics of head trauma. In: Miller L and Hayes R, eds. Head trauma therapeutics: basic, preclinical and clinical aspects. New York, NY: John Wiley and Sons, 2001.
[5] Alexander MP. Mild traumatic brain injury: Pathophysiology, natural history, and clinical management. Neurology, 1995;45: 1253-1260.

Now that at least 28% of the veterans of the current war are suffering from mild to moderate TBI, often accompanied by Post-Traumatic Stress Disorder (PTSD) the lack of treatment has become a significant public health concern. The DoD has now admitted that there are at least 360,000 mTBI sufferers, with potentially 45,000 to 90,000 having identifiable PCS symptoms.[6]

History of HBOT Leading to the Present Study

Despite the long history of HBOT's application to chronic wounds there has been limited application to chronic central nervous system wounds until the past 18 years. The previous paradigm that there is no treatment for brain injury hampered examining HBOT's potential for treating this condition. This was due in part to the failure to appreciate the sensitivity of chronic central nervous system (CNS) injury to lower pressures of HBOT (HBOT 1.5 or 7.35 psig v. HBOT 2.4 or 20.6 psig.)

In 1990 Dr. Paul Harch and colleagues applied low pressure dosing to divers with subacute, chronic, and neurological residua of cerebral decompression illness (DCI). Success with this group led to a broader application to hundreds of patients with a variety of cerebral conditions in an unfunded pilot series. The diagnosis which responded nearly equally to decompression illness was the PCS of mild TBI. It was theorized that the microscopic foci of damaged tissue in both conditions was the common basis. To verify the clinical experience Dr. Harch and colleagues duplicated the human results in a chronic focal cortical contusion animal model in 1996, then replicated the findings in 2001.

HBOT as used by the team is currently in use for 13 FDA-cleared indications by hundreds of physicians at nearly 1,000 locations across the nation, delivering approximately 10,000 treatments per day. The thirteen accepted indications for HBOT treatment include:

1. Air or gas embolism.
2. CO poisoning, CO poisoning complicated by cyanide poisoning
3. Clostridial myositis and myonecrosis (gas gangrene)
4. Crush injury, compartment syndrome, and other acute traumatic ischemias
5. Decompression sickness
6. Enhancement of healing in selected problem wounds
7. Exceptional blood loss anemia
8. Intracranial abscess
9. Necrotizing soft tissue infections
10. Osteomyelitis (refractory)
11. Radiation tissue damage (soft tissue and bony necrosis)
12. Skin grafts and flaps (compromised)
13. Thermal burns[7]

Scientific Basis for HBOT's Clinical Effects

Hyperbaric Oxygen Therapy (HBOT) has been used to treat a variety of human ailments for

[6] USA Today, "360,000 Vets May Have Brain Injuries," Greg Zoroya, Updated 3/5/2009 2:08 PM

[7] Hyperbaric Oxygen Therapy: 1999 Committee Report. Editor, N.B. Hampson. Undersea and Hyperbaric Medical Society, Kensington, MD. See also: Harch PG. Application of HBOT to acute neurological conditions. Hyperbaric Medicine 1999, The 7th Annual Advanced Symposium. The Adams Mark Hotel, Columbia, South Carolina, April 9-10, 1999; and Mitton C, Hailey D. Health technology assessment and policy decisions on hyperbaric oxygen treatment. Int J of Tech Assess in Health Care, 1999;15(4):661-70.

over 70 years[1]. Advancements in biomechanical research and cellular biology have allowed the mechanisms of healing with hyperbaric oxygen to become better understood and have shown that the primary action of HBOT occurs in the DNA of damaged cells. The overall effect of HBOT results in the growth of new cells, repair of damaged cells, increase in connective tissue, bone, and skin, and the healing of wounds regardless of their location in the body[1]. Based on the similarities in disease process of acute and chronic wounds and acute and chronic brain injury, applications of HBOT have been successfully extended to treat non-healing/chronic traumatic brain injuries and the neurological sequelae of such injuries.

HBOT is a non-invasive and non-pharmaceutical way to repair damaged tissue. The positive effect that HBOT has on the tissue repair is the result of two oxygen-dependent processes; the activation of cellular mechanisms and growth factors at the DNA level and the improvement of blood supply to poorly perfused tissues. The increased oxygen also greatly enhances the ability of white blood cells to kill bacteria and reduces swelling. As a result, HBOT positively impacts, and is approved to treat some of the most difficult and costly health disorders such as; gas gangrene, crush injuries, acute traumatic ischemias, air or gas embolism, decompression sickness (DCS), necrotizing fasciitis, osteomyelitis, chronic wounds, and radiation wounds. HBOT is also approved to treat the following three neurological disorders: intracranial abscess, carbon monoxide poisoning and neurological DCS.

The positive effects of HBOT on tissue repair occur regardless of the location of the wound(s) in the body. Accordingly, when correctly dosed, HBOT acts on non-healing brain injuries in much the same manner as with more visible non-healing wounds on the body (e.g., diabetic foot wounds, irradiated tissue wounds). In 1977, Holbach and Wassmann discovered that lower doses of HBOT (i.e., 1.5 ATA compared to 2.4 to 2.6 ATA typical in wound care) resulted with positive effects on brain metabolism[11]. Using glucose metabolism as a marker, the researchers discovered that oxygen in the brain is best optimized at 1.5 ATA. Amounts over that dose in the brain cause glucose metabolism to become dysfunctional. Dr Neubauer and Harsh who have collectively and successfully treated hundreds of brain-injured patients following the lower dose protocol have supported Holbach and Wassman's findings [12,13]. Therefore, while most HBOT treatments for standard wound care are administered at 2.0 – 2.4 ATA, clinical experience and scientific study show that the brain is more responsive to oxygen at a lower 1.5 ATA dose (HBOT 1.5).

The Science Behind HOBT: Cellular Effects

Neurons are exquisitely sensitive to any change in oxygen concentration, whether offered as hypoxia (lack of oxygen) or any form of hyperoxia (excessive oxygen) such as an oxygen enriched environment, hyperbaric air, or hyperbaric oxygen. A change in oxygen concentration results in gene transcription by the neuron, especially in stress responses, transport/neurotransmission, and signal transduction[14]. Thousands of affected genes have been identified[15]. Hypoxic conditions in the brain can also cause other problems such as[76]:

- Inhibited protein synthesis (a process by which DNA encodes for the production of amino acids and proteins necessary for life) accompanied by selective gene expression .
- Selective neuronal loss due to the generation of lactic acid in the brain (lactic acid is a byproduct of anaerobic activity).

- Induced glutamate release- an excitotoxic amino acid that can cause neuronal death by excessive stimulation.
- Tissue acidosis (excessive acid in body tissues), and declines in tissue phosphocreatine and ATP levels, the body's primary energy source.
- Infarction, or tissue death due to lack of oxygen.

HBOT however, has been found to serve as an effective antidote to the hypoxic damage experienced by the brain. The benefits are outlined as follows:

- Several studies have identified HBOT as a direct or indirect DNA signaling agent[16,17].
- HBOT has numerous cellular mechanisms of action, which are neuroprotective and assist the injured brain to heal. These include: activation of ion channels, inhibition of hypoxia inducible factor-1alpha, up-regulation of Bcl-2, inhibition of MMP-9, decreased cyclooxygenase-2 activity, decreased myeloperoxidase activity, up-regulation of superoxide dismutase and inhibition of Nogo-A (an endogenous growth-inhibitory factor)[18].
- HBOT enhances mitochondrial recovery so that the cell's main power structures can once again convert energy into forms usable by the cell, and reduces apoptosis (programmed cell death) in hypoxic nerve cells[19,20].
- HBOT promotes neural stem cell activation and growth[21,22] so that new neurons can be formed, and this effect is seen in the hypoxic damaged brain[23,24,25].
- HBOT alleviates hypoxic induced myelin damage[26]. Myelin serves as an electrically insulating and protective layer over certain neurons and damage or dysfunction to the myelin can slow nerve impulses, mix them up and/or cause certain illnesses.
- HBOT also increases cellular ATP levels and cognitive recovery after concussive injury[27].

Cellular Effects Evidenced in Animal studies

Any change in oxygen concentration after brain injury affects a plethora of cellular mechanisms through gene regulation. Supplemental oxygen either at normobaric (normal atmospheric pressure) or hyperbaric pressures limits leukocyte aggregation and attenuates the inflammatory cytokine response to ischemic stroke through gene expression with 5,769 differentially expressed genes identified[29]. Hyperoxia, induced by a hyperbaric oxygen therapy significantly enhances the mobilization of endothelial progenitor cells from the bone marrow into peripheral blood, leading to enhanced wound healing[30]. In neonatal rats subjected to ischemic injury, HBOT enhances the migration of neural stem cells to the brain cortex and differentiation into mature neurocytes[31]. HBOT significantly enhances learning and memory when compared to sham-treated controls[32]. Prior to injury, HBOT offers neuroprotection through inhibition of the p38 phosphorylation pathway regulating cellular apoptosis and inflammatory gene transcription[33]. After hypoxic injury, HBOT can suppress apoptosis if administered within two hours; if administered after a delay it is still effective with increasing effectiveness as the number of hyperbaric treatments increase[34]. After hypoxic injury HBOT increases neuronal synaptic transmission efficiency, and improves central nervous electrophysiological conduction velocity and reduces neuronal death[35]. Balance beam scores in rats with cerebral contusions were improved after treatment with HBO[36]. In a focal cortical contusion model, Harch et al demonstrated improved cerebral vascularization and cognitive

function through low pressure (1.5 ATA) HBOT[37]. These animal results correlate well with the clinical effects detailed below.

Clinical effects

While the healing effects of HBOT in the acute treatment of decompression illness have been known for decades, the condition of the injured brain after the acute phase of illness was thought to be more or less "permanent"[38]. However, Harch et al have demonstrated the efficacy of HBOT at 1.5 ATA (HBOT 1.5) in healing decompression sickness brain injury late after injury in the chronic phase of illness [39,40,41,42]. Importantly, clinically stable divers with residual brain injury from decompression sickness had a significant positive response to HBOT 1.5, even when their condition was thought to be unchangeable[43]. HBOT has been shown to be clinically effective in mediating the effects of brain injury[44]. For example, Lin et al randomly included 22 TBI patients into a HBOT group while the other 22 corresponding condition patients were assigned into a matched control group. Results evidenced that the HBOT group showed significant improvement in Glasgow Coma Scores and in Glasgow Outcome Scores[45]. Rockswold has also demonstrated improvement in the Glasgow Coma Scale as well as reduced mortality in acute TBI patients undergoing HBOT with minimal risk[46,47]. HBOT 1.5 in this group of acute patients appears safe and does not produce oxygen toxicity[48.]

The positive effects of HBOT occur even if treatment occurs months to years after the initial injury. A number of clinicians have demonstrated that HBOT 1.5, when used late after brain injury from a variety of causes (cerebral palsy, hypoxia, carbon monoxide, drowning, and stroke) is capable of promoting clinical improvement. Wright et al treated two airmen injured in roadside explosive blast four months after the initial injury with HBOT 1.5. Upon completion of the hyperbaric treatments nine months after their initial injury, both showed improvement in all measured areas, with most measures improving to pre-injury baseline levels (see Attachment 1). Hoggard et al treated a brain-injured patient 15 months post-injury. Pre-test and post-test measures for speech, language and cognitive deficits were obtained. The patient demonstrated improvement in all three measured areas[49]. Hardey et al found that HBOT improved neuropsychological and electrophysical improvements in a chronically brain injured patient one year post-injury[50]. In sum, the number of reports and cases demonstrating the repeatedly beneficial effects of HBOT 1.5, when applied late after initial brain injury, makes it seem quite unlikely that these effects are mere chance[51,52,53,54,55,56,57,58,59,60,61].

An additional benefit to HBOT is that the treatment is safe with very few negative side effects. The most commonly reported side effect is barotrauma to the soft tissues such as the ears and sinuses, also known as a "squeeze", but these are easily dealt with both prior to and during treatment. HBOT is also often less expensive than current treatments for mTBI and PTSD, which only treat the symptoms and not the underlying disorder or injury. Further, as discussed above, the mechanisms of action of HBOT are now well understood in the scientific literature, providing justification for the treatment of certain disorders and injuries.

Traumatic Brain Injury

Recent research has demonstrated the efficacy of HBOT for traumatic brain injury, both when

then treatment was administered early and late after the initial injury. In acute severe TBI, HBOT has been shown to be effective in reducing mortality[62]. Harch et al. demonstrated consistent SPECT brain imaging improvements (showing improved brain blood flow) in chronic mTBI patients treated with HBOT 1.5[63,64,65,66] (see Attachment 2). Since the original work of Dr. Neubauer and Harch, the efficacy of HBOT 1.5 in chronic stable mTBI has been well documented[67,68]. Patients with abnormal SPECT scans showing abnormal brain blood flow in mTBI show consistent improvement after HBOT 1.5[69]. To date Dr. Harch has treated more than 60 mTBI patients with HBOT 1.5 showing consistent, and sometimes dramatic, clinically relevant improvements. Using the identical HBOT 1.5 protocol in an unrelated center in Florida, Dr. Eddie Zant has achieved similar results - improvement in all of 17 military and former military TBI patients. Many patients were unable to work in their military occupations or to attend college. All those working were able to retain their military or civilian jobs and those who had dropped out of college courses were able to resume their studies after treatment. Similarly, Dr. Harch recently reported dramatic improvement in a series of 15 patients treated with HBOT 1.5 in a clinical trial of military acquired mTBI (see Attachment 3). Other individual trials also have demonstrated the efficacy of HBOT 1.5 for chronic stable mTBI[71]. A 310 patient Chinese trial demonstrated improvement clinically, in neuropsychiatric testing, as well as in SPECT scans after HBOT 1.5[72.] In a randomized controlled trial of 21 brain-injured adults, HBOT 1.5 resulted in improved neuropsychiatric testing for the treated group[73].

HBOT General Safety Profile and Extra Safety of HBOT 1.5 ata

The HBOT 1.5 protocol is extremely safe[8] and effective, and is a direct extension of the U.S. Navy Diving Tables. In the United States Navy as well as the world navies injured divers are treated for decompression sickness shortly after emerging from the water and experience a 90% cure rate on the first treatment. Those who do not have complete remission are treated repetitively with a tapered dose of HBOT until they reach a treatment plateau. Unfortunately, injured commercial divers and recreational scuba divers have hours to days delay to treatment and are often left with significant neurological residual damage.

In the late 1980s Dr. Harch used the Navy concept of tapered dose to extend the Navy dive tables and found that commercial and SCUBA divers neurologically improved far after plateau on the U.S. Navy protocol. Divers with residual neurological injury months to years after typical U.S. Navy treatment also improved. These findings were then successfully applied to over 60 other chronic neurological conditions, including TBI and PTSD. Essentially, this protocol was derived by simply reducing the oxygen pressure from 2.4 ATA [Atmosphere Absolute or 20.6 pounds per square inch-gauge (psig)], commonly used in wound care, to 1.5 ATA (7.35 psig). This 38% reduction in dose of HBOT was found to be not only safe (could repair seizures instead of causing them), but also effective on both sub-acute and chronic neurological wounds.

In an extensive longitudinal study of HBOT complication rates in San Antonio civilian

[8] DoD "HBOT for TBI" Consensus Conference White Paper, 28 October 2008.

multiplace facilities from 1979 through 2001, 8,229 patients received 170,096 exposures to hyperbaric oxygen, from 6.0 ata to 2.36 ata. There was a 1% complication rate over 22 years. There were no fatalities. (Note: The lowest dose in these treatments is nearly 3 times the amount of oxygen per treatment in this NBIRR observational study.) "The top 10 reasons for removal from the chamber were: ear barotraumas (45/10,000 exposures), sinus barotraumas (8/10,000 exposures), claustrophobia/anxiety (7/10,000 exposures), abdominal pain/diarrhea (5/10,000 exposures), nausea/vomiting (5/10,000 exposures), chest pain (3/10,000 exposures), unable to autoinflate ears despite PE tubes (2/10,000 exposures), refusal to continue treatment (2/10,000 exposures), seizure (2/10,000 exposures), and doctors/other appointments (1/10,000 exposures)." The conclusion of the paper states, "In this large patient series, the incidence of complications requiring removal from oxygen or removal from the chamber was very low (approximately one percent of exposures). The occasional potentially life-threatening events were appropriately managed without fatality by fully trained, competent staff."[9]

Gaylan Rockswold, M.D., the neurosurgeon who reduced death by 59% in the most fragile of acutely brain injured patients wrote, "Based on our own past and continuing investigations … placing severe TBI patients in either a monoplace or multiplace HBO chamber at 1.5 ATA for 60 minutes is a very low risk procedure."[10] In 2000, the American Academy of Pediatrics published a response to another article outlining that 35,000 cases of LPHBOT (HBOT 1.5), was a minimal risk medical treatment.[11]
The official DoD White Paper states, "Side effects from HBOT are uncommon, and severe or permanent complications are rare, especially at the doses of HBOT used "off-label" for TBI patients (approximately 1.5 atm abs for 60 minutes), compared to HBOT for HHS-covered indications (2 to 2.4 atm abs for 120 to 90 minutes)."[12] For the mild traumatic brain injury patient, clinical experience demonstrates this treatment is far less risky to patients than leaving them untreated (currently subject to high suicide rate, homelessness, disability, incarceration, and aberrant violent behavior.) It is also less risky than being in Iraq or Afghanistan.

Preliminary results from the pilot study protocol (LSUHSC IRB Protocol #7051) approved by Louisiana State University's IRB to treat 30 veterans of the war, 15 with TBI and 15 with TBI/PTSD, have demonstrated that blast-injured war veterans respond very positively to HBOT 1.5. There have been NO adverse events or side-effects. Clinical symptoms on the Rivermead Post-concussion Symptoms Questionnaire[13] have shown a 40% reduction in symptoms on a majority of patients. Further, a majority of casualties treated have recorded

[9] Sheffield, P.J.; Sheffield, J.C.; "Complication Rates for Hyperbaric Oxygen Therapy Patients and their Attendants: A 22-year Analysis," Proceedings of the Fourteenth International Congress on Hyperbaric Medicine, San Francisco, California, USA, Editors: Fredrick S. Cramer, Paul J. Sheffield. pp. 312-318 (Appendix III).
10 Rockswold, Sarah B; Rockswold, Gaylan L.; Neurological Research, Vol. 29, March 2007, pp. 162 – 172.

[11] Harch, Paul G., M.D.; Deckoff-Jones, Jamie, M.D.; Neubauer, Richard A., M.D. 12 Feb 2001 (response), "Low Pressure Hyperbaric Oxygen Therapy for Pediatric Brain Injury, A Minimal Risk Medical Treatment." *Pediatrics*(ISSN 0031 4005) Copyright © 2000 by the American Academy of Pediatrics
[12] DoD "HBOT for TBI" Consensus Conference White Paper, 28 October 2008.
[13] This Questionnaire is the standard measure of post concussion injury and was selected by the DoD HBOT Consensus Conference as the measure they were going to use to determine clinical effectiveness. A 10% reduction is considered significant. All HBOT 1.5 treated veterans have had between 13% and nearly 43% improvement on this scale. See King, N., Crawford, S., Wenden, F., Moss, N., and Wade, D. (1995) J. Neurology 242: 587-592, available at:
http://www.wsib.on.ca/wsib/wsibobj.nsf/lookupfiles/pocmtbirivermead/$file/mtbi_rivermead.pdf

a 20+ point IQ jump, and most have experienced a 40% decrease in PTSD symptoms, just with the first ½ of the protocol. This study is underway and still recruiting patients. Everyone receives treatment and recruiting and treatment are being completed as quickly as possible so that data can be utilized by policy makers striving to solve the national crisis these untreated casualties are adding to the other challenges the nation is facing.

HBOT 1.5 Safety Compared to Drugs Prescribed Off-Label for PCS & PTSD

When comparing HBOT to the common drugs being prescribed off-label for PTSD and TBI patients, the difference is remarkable. (Only Zoloft is 'FDA-labeled' for PTSD. None are approved for PCS or TBI) Many of the anti-depressants have a warning label from the FDA. The actual FDA warning reads, "Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidal) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of (insert name of antidepressant) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24…" The age group described by this warning would seem to include a significant number of our brain-injured veterans. Thus, by getting this study done quickly, the investigators have a good chance of helping reduce the epidemic of suicides in the current population of casualties from the current war.

Animal Research Verifies Human Treatment Experience

It is well to note that animal studies utilizing the HBOT 1.5 protocol have now replicated the experience with HBOT 1.5 in humans. This is the first improvement of chronic brain injury in animals in the history of science. A copy of this research report, "Hyperbaric Oxygen Therapy Improves Spatial Learning and Memory in a Rat Model of Chronic Traumatic Brain Injury" is at www.HyperbaricMedicalAssociation.org/Science .

The Impact of TBI

TBI is a disorder of major public health significance. Each year in the United States there are 100 new cases/100,000 population and 52,000 deaths with the highest incidence in the 15-24 and over 75 years old age groups.[14] Most patients survive and add to an increasing prevalence of patients with chronic TBI, estimated at 2.5-6.5 million individuals in 1998.[15] All of these figures grossly underestimate the scope of the problem for at least two reasons: 1) Reporting bias against mild TBI. The aforementioned figures are based exclusively on information about hospitalized patients and those who die before hospitalization, i.e., moderate and severe TBI. These groups represent only 15-25% of the total TBI population[16]; and 2) Significant under diagnosis of mild TBI; 20-40% of patients with mild TBI never seek medical attention.[17] More accurate figures a decade ago for mild TBI were

[14] NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. Rehabilitation of Persons With Traumatic Brain injury. JAMA, September 8, 1999; 282 (10): 974-983.
[15] Ibid.
[16] Alexander MP. Mild traumatic brain injury: Pathophysiology, natural history, and clinical management. Neurology, 1995;45: 1253-1260; Kraus JF, Nourjah P. The epidemiology of mild uncomplicated brain injury. J Trauma. 1988;28:1,637-1643.
[17] Frankowski RF, Annegers JF, WhitmanS. The descriptive epidemiology of head trauma in the United States. In: Becker DP, Povlishock JT, eds. Central Nervous System Trauma Status Report. Bethesda, MD: National Institute of Neurological and Communication Disorders and Stroke, National Institutes of Health; 1985.

180/100,000 population.[18] Consequently, mild TBI has been characterized as a "hidden epidemic."[19]

Despite different definitions of mild TBI[20], 15-29% of the mild TBI populations have appreciable complaints 6 months after injury.[21] These ongoing symptoms are PCS[22] and this syndrome is associated with a high degree of morbidity and unemployment.[23] At one year the incidence declines slightly to 10-15%, but many of these individuals are at risk for developing the persistent PCS, a syndrome of organic and psychiatric pathology.[24] Both of these syndromes (collectively referred to as PCS in this application) have long-term cognitive, social, emotional, and psychological dysfunction[25] that our proposed treatment may address.

TBI is the leading cause of long-term disability in children and young adults. Patients experience disruption in health, cognition, behavior, emotional function, social function, work, school, and family life with a resultant substantial economic toll. This economic toll was estimated in 1998 to be $9-10 billion/year for acute care and rehab of new cases. Lifetime costs of care are much higher and remarkably underestimated by exclusion of lost earnings, costs to social service systems, and the value of the time and foregone earnings of family members who care for persons with TBI.[26] One source estimated the direct and indirect costs at $56 billion in 1995.[27] Due to the low inclusion rate of mild TBI in all of the above statistics, the costs of chronic mild TBI or PCS are difficult to estimate, but most likely substantially increase the aforementioned costs.

Unfortunately, there is no cure for the residual effects of TBI and PCS despite the application of a wide range of rehabilitation strategies, including cognitive rehabilitation,[28] pharmacologic therapy[29], and others. In fact, treatment failures are common 3-6 months

[18] Kurtzke JF, Kurland LT. The epidemiology of neurologic disease. In: Joynt RJ, ed. Clinical neurology, rev. Philadelphia: JB Lippincott, 1993:chap 66.
[19] Gordon WA, Brown M, Sliwinski M, et al. The Enigma of "Hidden" Traumatic Brain Injury. J Head Trauma Rehabil, 1998; 13(6): 39-56.
[20] Ruff RM, Jurica P. In search of a unified definition for mild traumatic brain injury. Brain Injury, 1999; 13(12): 943-952.
[21] Bohnen N, Twijnstra A, Jolles J. Persistence of postconcussional symptoms in uncomplicated, mildly head-injured patients: a prospective cohort study. Neuropsychiatry Neuropsychol Behav Neurol, 1993; 6: 193-200.
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post injury.[30] There is in fact no ICD-9 code for Traumatic Brain Injury or Coma. This is reflective of the belief that there is no treatment for these conditions. This has caused a great deal of confusion in the military medical system where a TBI patient will be labeled as a PTSD patient when they do not have PTSD symptoms simply because there is an ICD-9 code for PTSD.[31]

A 1998 NIH Consensus Development Conference on Rehabilitation of Persons with Traumatic Brain Injury reported that "a critical analysis of the literature on TBI rehabilitation yields only a few studies that suggest effectiveness under limited conditions."[32] They felt that TBI rehabilitation research was exceedingly difficult to conduct and obtain funding for and that a major limitation was the narrow focus on restorative approaches which were either adaptive or enabling (NIH Consensus). Little or no attention has been directed to the problem of biological repair of the underlying chronic TBI wound. From the LSUHSC IRB #7051 results, HBOT 1.5 may hold the answer to the repair of chronic CNS wounds.[33]

In addition, the NIH Consensus Conference noted that rehabilitation should include cognitive and behavioral assessment and intervention and that special programs are needed to identify and treat persons with mild TBI. They recommended that research include: 1) Well designed and controlled studies of the effectiveness of interventions; 2) Development and study of innovative rehabilitation interventions; 3) Testing of promising treatments of TBI derived from animal studies; 4) Study of the neurobiology of TBI in humans with modern imaging techniques and correlation of these with neuropsychological findings; 5) Evaluation of the relationship between specific cognitive deficits and global outcomes, and 6) Validation of generic health-related quality of life assessment instruments for use in TBI.[34] This trial and other trials currently being studied by Dr. Harch will address these recommendations.

Pathophysiology of TBI

TBI is a complicated heterogeneous diffuse cerebral insult characterized by primary mechanical disruption of tissue[35] and secondary injury from ischemia,[36] hypoxia[37], edema[38],

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vasospasm[39], neurochemicals,[40] and reperfusion injury.[41] Both acute and chronic injury exists on a spectrum with resultant tissue pathology that is proportional to the severity of injury[42], and is commonly classified as mild, moderate, or severe. Mild TBI has been defined in multiple ways[43] using various combinations of signs, symptoms, and laboratory criteria. The lack of a consensus definition[44] has led to wide variability in research findings due to inclusion of patients with different degrees of mild TBI. The underlying problem appears to be the inability to readily document a specific pathological correlate of mild TBI. Because of the lack of an anatomic barometer the characterization of chronic symptoms resulting from mild TBI suffer from the same problem. Specifically, there has been a long-standing organic vs. functional argument[45] over the existence or degree of anatomical pathology for persistent symptoms after mild TBI, the post-concussive syndrome[46].

In the past 20 years with better diagnostic tools, opinion has shifted in the direction of implicating organic injury in the pathogenesis of mild TBI[47]. Multiple studies have reported gray and white matter injury in animal and human acute mild TBI[48]. The pathological

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findings have also been captured on anatomic and functional imaging studies and the imaging abnormalities felt to act as surrogate markers of tissue injury. In a non-impact TBI pig study[49], for example, histological areas of damage were highly correlated with abnormal T2 MRI findings. This ability to image tissue injury in TBI is dependent on the sophistication of the imaging modality. As the sophistication of the imaging modality has increased, the incidence of abnormalities in acute mild TBI has simultaneously increased. For example, CT has had poor sensitivity for mild TBI[50] while MRI[51], magnetization transfer imaging (MTI)[52], magnetic resonance spectroscopy (MRS)[53], and SPECT[54] have demonstrated a greater incidence of abnormalities. This increased sensitivity was mirrored by the findings in Kimura's[55] swine model. Magnetization transfer ratio analysis of conventional MRI imaging in normal areas of T2 signal showed a significant correlation with anatomic white matter damage. In essence, both anatomic and functional imaging findings are increasingly felt to represent tissue injury.

The acute pathology of mild TBI matures with time and results in downstream synaptic loss[56], nerve cell loss[57], and overall tissue loss[58]. The underlying organic pathology in mild

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TBI can be unmasked by hypoxic stress[59]. In this study asymptomatic mild TBI patients demonstrated a significant decrement in neuropsychological performance compared to baseline testing when subjected to the hypoxia of an equivalent 3,800 meter elevation. These results implied an organic compromise of the functional reserve capacity of the injured brain[60]. Such a reduction in reserve capacity is supported by Hofman et al[61] who demonstrated atrophy of the brain months after mild TBI and McAllister's findings of changed activation circuitry patterns on functional MRI to increasing working memory processing loads in mild TBI patients one month post injury[62]. Reduced reserve capacity has also been shown in studies of multiple concussion patients[63]. Those patients with an acute concussion after one or more non-disabling prior concussions displayed evidence of previously unidentified or unappreciated damage from the prior concussions[64]. The net conclusion of this pathological and imaging literature is that mild TBI causes organic brain injury that is persistent.

Mild TBI has Permanent Effects - 90% of Concussions Do Not "Heal" in Six Months

The doctrine that the brain adjusts to a concussion in 90% of concussive sports injuries and neuropsych test scores return to near normal, assumes there are no further injuries to these athletes. A second injury is known to prevent recovery. This is why the "readiness to play" concept has become standard practice and the IMPACT automated neuropsychological test was developed. The assumption, that these battle casualties are the same as sports concussions is an incorrect model for this application. These battle casualties have successive concussions within a six month period that prevent recovery. Further, blood brain flow does not return to normal in athletes as previously believed. A new article in Brain: A Journal of Neurology published by Oxford, now shows that 30 years post injury there is not the recovery that had previously been reported. They state, "There is a growing body of evidence suggesting that there are cumulative effects of concussions that manifest as increased susceptibility to subsequent concussions as well as an increase in their severity. More recent findings suggest that the effects of a concussion far outlast the acute phase." They further point out that there is an earlier onset of mild cognitive impairment and an earlier onset of Alzheimer's disease. Thus for military medicine and policy makers to assume "90% of concussed veterans get better in six months with no treatment" is simply not true and has prevented effective treatment from being explored.[65]

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Further, brain blood flow is decoupled even in these sports concussions.[66] Even though neuropsychological tests show a return to normal cognitive function, brain blood flow in these individuals remains decoupled. The brain is not able to control its blood circulation as it did previously. Drs. Rockswold, Harch, Orrison, and Fogarty have now all demonstrated that HBOT 're-couples' brain-blood flow, with even a single hyperbaric treatment, thus restoring the physiology in the brain that helps start a healing process.[67]

Heterogeneity of Trauma-related Organic Brain Injury Pathophysiology and Loss of Conciousness

Despite the evidence for organic pathology in acute mild TBI, identification of the pathological substrate for symptoms or signs has been difficult. Loss of conciousness (LOC), however, appears to be a marker of acute tissue injury that also correlates with subsequent tissue loss in both animals and humans. Jane identified the pathology of seven day old animal concussion characterized by LOC as brainstem white matter injury[74]. Kotapka demonstrated that similar transient unconsciousness (less than 15 minutes) caused hippocampal lesions in 46% of animals from 4 hours to 15 days post injury.[68] In humans LOC has been linked to both imaging abnormalities and tissue injury. Both Jenkins[69] and Hofman[70] have shown brain lesions on MRI in 100% of patients with loss of consciousness of less than 5 minutes, and 57% with Glascow Coma Scale (GCS) of 14-15 and less than 20 minutes loss of consciousness, respectively. In Hofman's study all of the patients with acute MRI or SPECT findings showed brain atrophy on repeat MRI six months later manifest by an increased ventricle/brain ratio, indicating primarily white matter loss. It appears from these studies that acute MRI or SPECT findings in patients with mild TBI and LOC seemed to be surrogate markers for tissue injury sufficient to produce infarct. Similarly, MacKenzie[71] showed whole brain atrophy on repeat MRI at least 3 months apart in mild to moderate traumatic brain injury. Those patients with LOC had greater atrophy. Neuronal loss has also been found on post mortem examination of patients with "concussion" by both Lidval[72] and Symonds[73]. In summary, acute LOC in mild TBI is associated with abnormal imaging findings and tissue injury that results in later tissue loss. Because of the data establishing organicity of LOC in mild TBI, LOC will be an inclusion criterion in our study.

In addition to brief LOC, (less than thirty minutes), there may also be a period of confusion or amnesia lasting less than 24 hours.[74] The NBIRR physician team has seen a number of patients who have never suffered a loss of consciousness after a blast exposure, or who have no memory of having suffered a period of unconsciousness. The Glasgow Coma Scale is 13 to 15 and imaging studies are also usually normal. Since the symptoms of mild

[66] Tegeler CH, et. al, "Dynamic Vascular Assessment of Brain Circulation for Sports-Related Concussion."

[67] See HBOT 1.5 Restores brain Blood Flow & Metabolism, N-BIRR Casualty Case Reports.

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TBI may develop gradually, are often subtle, and can be confused with other illness such as PTSD, mTBI may be unrecognized and undiagnosed[75]. A concussive injury causes diffuse axonal injury, structural neuronal damage, and diffuse neuronal dysfunction.[76] The symptoms of mild TBI are variable and may include headache, irritability, impulsivity, anger, cognitive impairment, memory difficulty, loss of executive function, vestibular and sleep disturbances.[77] Electroencephalogram and sleep studies are usually normal.

Post Concussion Syndrome (PCS)

A significant proportion of mild TBI patients will have persistent symptoms one year after injury, which represents PCS. One author's review reports 8-32% of subjects with residual headaches, 4-25% with memory loss, and 19-25% with dizziness[78] while another suggests 7-8% with symptoms and 14% disabled from work[79]. At least two sources[80] define the PCS in terms of significant head trauma, symptoms, neuropsychological deficits in memory or attention, and social or occupational dysfunction. Similar to the acute symptoms in mild TBI the late symptoms and neuropsychological abnormalities in PCS have been shown to correlate with imaging abnormalities. Lewine[81] has demonstrated that 65% of patients with persistent post-concussion symptoms had abnormal magnetic source imaging. The imaging abnormalities suggested at least partially reversible or compensated injury since they directly correlated with symptom resolution. Hofman[82] found that slower reaction times in patients with persistent neurocognitive symptoms significantly correlated with abnormal MRI findings at 6 months post mild TBI. Voller[83] reported that 25% of patients with very mild TBI (GCS 15) and significant impairment in verbal memory, arithmetic ability, and psychomotor reaction time six weeks post injury had abnormal MRI's. Kesler and colleagues[84] noted a significant correlation of memory and intellectual impairment several years post all severities of TBI with the number of abnormalities on MRI and quantitative MRI individually and the combination of MRI, quantitative MRI, and SPECT. The incidence of abnormalities on each imaging modality varied between 51 and 62%. Neuropsychological impairment has also been shown to correlate with MRS abnormalities. In a collection of TBI patients of varying severities, MRS at an average of 53 days post TBI revealed that the NAA/creatine ratio in white and gray matter was significantly associated with composite neuropsychological dysfunction[85]. The authors felt that MRS

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[80] Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR), 2000. Appendix B, Criteria Sets and Axes Provided for Further Study: Postconcussional Disorder, 760-762.
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measurements reflected the behavioral manifestations of neuronal dysfunction.

Similarly, neuropsychological deficits have been correlated with SPECT and PET abnormalities one month to years post TBI. Baulieu[86] found that all patients with neuropsychological deficits one year post TBI had SPECT abnormalities eleven months earlier. Memory deficits specifically correlated with left brainstem/ and basal ganglia/cerebellar ratios. Laatsch[87], in a small series of patients, reported SPECT and neuropsychological deficits in 100% of patients an average of 20 months post mild-moderate TBI (GCS 11-15). They noted that the SPECT deficits generally correlated with the neuropsychological impairments and improved on SPM analysis as the neuropsychological deficits improved during cognitive rehabilitation therapy. A similar correlation between neuropsychological abnormalities and SPECT abnormalities has been demonstrated by Ichise[88] in both mild and major TBI patients referred for neurorehabilitation six months post injury. Umile[89] documented verbal or visual memory deficits in 95% and functional imaging (PET, SPECT) findings in 90% of mild TBI patients with persistent post-concussion symptoms. 75% of these patients had abnormal medial temporal lobe results on PET and SPECT. Correlation was established between neuropsychologic testing and functional imaging, but was not consistent across the entire group. MRI and/or CT scans at the time of injury were normal in 75% of patients. The conclusion from the literature on the sequelae of TBI and imaging is that persistent symptoms, i.e. PCS, and psychometric abnormalities resulting from mild TBI correlate with and are the reflection of organic injury to the brain acutely and chronically These findings, taken together with the data referenced above suggesting an organic basis for LOC in TBI, dictate that our study note those with LOC and differentiate between those mild TBI patients with acute LOC who also have demonstrated neuropsychological impairment, and those with no LOC but who demonstrate impairment on ANAM, report by military command, or independent neurological evaluation.

The Department of Defense invited William W. Orrison, Jr., M.D., to present the radiology presentation on December 5th, 2008 at the "HBOT in TBI" Consensus Conference. The Harch SPECT brain image of a Marine with six IEDs and an RPG hit is attached.[90] At Dr. Orrison's presentation, he showed three patients' whole brain CT scans, from his practice, who had been treated with the Harch HBOT 1.5 protocol by 3 different physicians. All patients had major recovery of brain function and neural structures. Here is his quote regarding Dr. Harch's SPECT brain images: "Dr. Harch's use of SPECT brain imaging to examine the changes in the brain before and after hyperbaric oxygen therapy is scientifically accurate and valid. Multi-detector SPECT imaging is one of the only neuroimaging methods with sufficient utility to allow this type of longitudinal evaluation.The improvement in brain perfusion demonstrated by Dr. Harch pre and post HBOT is

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[87] Laatsch L, Pavel D, Jobe T, Lin Q, Quintana JC. Incorporation of SPECT imaging in a longitudinal cognitive rehabilitation therapy programme. Brain Injury, 1999;13(8):555-570.
[88] Ichise M, Chung D-G, Want P, et al. Technetium-99m-HMPAO SPECT, CT and MRI in the Evaluation of patients with Chronic Traumatic Brain Injury: A Correlation with Neuropsychological Performance. J Nucl Med, 1994;35:217-226.
[89] Umile EM, Sandel ME, Alavi A, et al. Dynamic imaging in mild traumatic brain injury: support for the theory of medial temporal vulnerability. Arch Phys Med Rehabil, 2002;83(11):1506-13.
[90] Examples of some of the hundreds of patients Harch has treated with HBOT 1.5 over the past 20 years are at www.HyperbaricMedicalAssociation.org/Science.

impressive and objective evidence of improved cerebral blood flow in these patients. This is the same type of change that we have recently demonstrated using the new method of whole brain CT. In addition, the clinical observations and neuro-psych testing done by numerous physicians at different locations further verifies Dr. Harch's results and correlates with the objective findings observed on the SPECT images."[91]

Psychometric Testing

Neuropsychological measurement has been used as the gold standard in the differential diagnosis and functional evaluation of cognitive and neurobehavioral outcomes following TBI[92]. As mentioned above, DSM-IV TR[93] proposes inclusion of PCS based on new or worsening pre-existing attentional or memory symptoms, as well as the presence of more than two post-injury somatic and/or affective symptoms after sustaining a mild TBI. While this proposed disorder is controversial[94], some professionals have acknowledged mild TBI cases with persistent cognitive, somatic, or neurobehavioral symptoms that are consistent with PCS (APA 2000). As TBI may result from focal and/or diffuse injuries, different patterns of cognitive, neurobehavioral, and adaptive functional impairments would be expected and would contribute to heterogeneous courses and outcomes. To capture this well-known heterogeneity, we will use multiple pre- and post-treatment neuropsychological, neurobehavioral, and adaptive functional measures of the potential efficacy of HBOT treatment (Primary Specific Aim). Indeed, most of these measures have been recommended as valid outcome measures in TBI recovery or clinical trials research[95]. These measures also will be completed within the same week as completion of both pre- and post-HBOT functional imaging to permit relatively contemporaneous correlational analyses between pre- and post- neuropsychological, neurobehavioral, or adaptive functional outcome change scores and corresponding pre- and post-HBOT treatment functional imaging change scores (Secondary Aim).

The specific neuropsychological tests in this protocol were selected based on recent consensus recommendations for clinical trials for outcome research in TBI[96]. Other measures were selected to identify confounding disorders or conditions such as malingering and/or somatoform disorders that are frequently identified in patients with a

[91] William W Orrison Jr, MD, December 5th, 2008.
[92] Clifton G, Hayes R: Outcome measures for clinical trials involving traumatically brain-injured patients: Report of a conference. Neurosurg 1992;31:975-978; Levin H: Neurobehavioral outcome of closed head injury: implications for clinical trials. J Neurotrauma 1995;12:601-610.
[93] Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR), 2000. Appendix B, Criteria Sets and Axes Provided for Further Study: Postconcussional Disorder, 760-762.
[94] Williams DH, Harvey SL, Eisenberg HM. Mild Head Injury Classificationl Neurosurgery, 1990;27(3):422-428; Binder L, Rohling M, Larrabee G: A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. J Clin Exp Neuropsych 1997;19:421-431; Binder L: A review of mild head trauma. Part II: Clinical implications. J Clin Exp Neuropsych 1997;19:432-457; Satz P, Alfano M, Light R, et al: Persistent Post-Concussive Syndrome: a proposed methodology and literature review to determines the effects, if any, of mild head and other bodily injury. J Clin Exp Neuropsych 1999;21:620-628.
[95] Clifton G, Hayes R: Outcome measures for clinical trials involving traumatically brain-injured patients: Report of a conference. Neurosurg 1992;31:975-978; Levin H: Neurobehavioral outcome of closed head injury: implications for clinical trials. J Neurotrauma 1995;12:601-610.
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history of Mild TBI[97]. Recently Col Wright treated 2 airmen with HBOT 1.5 with pre and post deployment ANAM tests.[98] He noted that they had been misdiagnosed in their records as having PTSD when they demonstrated few of the symptoms.

Hyperbaric Oxygen Therapy Repairs Basic Pathophysiology

HBOT is the use of oxygen in an FDA-cleared medical device, a pressure chamber that uses oxygen at greater than atmospheric pressure as a medication or drug to treat basic pathophysiologic processes/states and the diseases in which they are manifest[99]. HBOT has drug effects on both acute and chronic tissue pathophysiology[100]. Chronically, HBOT is a trophic drug that exerts its effects in non-healing wounds that are often characterized by shallow perfusion gradients. The prototypical chronic wound model of HBOT is the head and neck soft tissue and osteoradionecrosis wound caused by external beam radiation. Repetitive HBOT in this model results in angiogenesis and healing[101], yet the intervening mechanisms have been poorly understood until recently. In the past six years these steps have been elucidated in a variety of basic science studies that have identified HBOT as a direct or indirect DNA signaling agent[102]. Through the action of repetitive intermittent exposure to hyperoxia DNA is signaled to begin transcription of various wound repair sequences that cause trophic tissue changes. Hyperbaric oxygen therapy has been shown not only to expedite wound healing by hastening angiogenesis, but it also increases or restores the bactericidal properties of polymorphonuclear lymphocytes and macrophages, speeds the migration of macrophages, and hastens wound epithelialization and contraction.[103] These effects have been clinically useful and proven for diabetic wounds, poorly vascularized tissue, infected tissue, osteomyelitis, and irradiated tissue[104]. In full thickness, skin grafts and flaps, hyperbaric oxygen has been shown to speed healing and enhance flap take and graft survival, especially when compromised.[105] In burn patients undergoing grafting procedures, hyperbaric oxygen has been shown to shorten hospital

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[97] Binder L, Rohling M, Larrabee G: A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. J Clin Exp Neuropsych 1997;19:421-431; Binder L: A review of mild head trauma. Part II: Clinical implications. J Clin Exp Neuropsych 1997;19:432-457.

[98] Colonel Wright, James K. (USAF, MC, SFS); Zant, Eddie; Groom, Kevin; Schlegel, Robert E. ; Gilliland, Kirby; Manuscript: Case report: Treatment of Mild Traumatic Brain Injury with Hyperbaric Oxygen: 2009 (Prepared for Military Medicine.)

[99] Harch PG, Neubauer RA (1999) Hyperbaric oxygen therapy in global cerebral ischemia/ anoxia and coma. In Jain KK (ed) *Textbook of Hyperbaric Medicine, 3rd Revised Edition, Chapter 18.* Hogrefe & Huber Publishers, Seattle WA 1999: 319-345.

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stay, enhance donor site and graft healing, and reduce the number of grafting procedures required for wound closure.[106] The salvaging effect of hyperbaric oxygen on failing flaps and full thickness skin grafts has been demonstrated in numerous studies.[107] Thus the treatment will also be very effective for residual damage from wounds these veterans have received on the battlefield, and these same mechanisms of healing can be expected to demonstrate the clinical effect seen in the LSUHSC IRB #7051 and the previous Level III, Level IV human studies, as well as the chronic brain injury animal work previously cited.

HBO is capable of favorably influencing a number of cytokines and growth factors integral to wound healing. When administered after wounding, HBO up-regulates collagen synthesis through pro-al (I) mRNA expression.[108] In rabbit ear wounds HBO has been shown to up-regulate mRNA for the PDGFβ □receptor.[109] This effect has been further born out in clinical studies. In ischemic flaps HBO up-regulates fibroblast growth factor(FGF) causing an increased effect over that seen with fibroblast growth factor alone.[110] In situations where FGF is ineffective, HBO can render it highly effective.[111] This is an effect different than up-regulation. In patients with Crohn's disease IL-1, IL-6, and TNFα □levels were diminished during HBO treatment.[112] TNF levels in normal rats became elevated after a single exposure to hyperbaric oxygen (HBO).[113] Perhaps under different physiologic conditions HBO may cause up or down regulation of cytokines. Vascular endothelial growth factor (VEGF) is upregulated by hypoxia, yet HBO also up-regulates this factor.[114] Transforming growth factor-β□(TGF-β1) and platelet-derived growth factor ββ (PDGF-β) are synergistically enhanced by HBO.[115]

HBO thus acts in a paradoxical manner. Many of the processes that are stimulated by hypoxia are accelerated by the administration of HBO. The following biologic processes and factors are stimulated or up-regulated by hypoxia, and by HBO: angiogenesis, collagen synthesis, and osteoclastic activity. One known mechanism is that by which fibroblasts are stimulated to make collagen through peroxides, which occur, in the hypoxic wound and during HBO treatment.[116] Therefore, the peroxides generated by HBO mimic one of the stimuli found in hypoxia. Another mechanism is the stimulation of cytokines by hypoxia and

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[116] Ibid.

further upregulation of these cytokines under the hyperoxia, which occurs during HBO treatment. This is the case for some interleukins and for tumor necrosis factor (TNF). There is some confusion on the exact timing of the release of growth factors and cytokines; in one study VEGF, TNF-α, and TGF-β occurred in hypoxic wounds after they had been released in normoxia. VEGF, TGF-β, and PDGF-β have bi-phasic release patterns; their release is stimulated by hypoxia and hyperoxia, but is lowest during normoxia.[117] Furthermore, the activity of released VEGF is further enhanced during hyperoxia, especially in the presence of lactate.[118] It is clear that biologically active chemicals such as cytokines and growth factors have a complex array of stimuli to up and down regulate activity. Oxygen, cytokines, and biologically active chemicals and metals appear to have key roles in the expression of healing.

As we learn more about the role of oxygen its role appears to be much more detailed than in a simple mass action equation. In reperfusion injury, HBO diminishes tissue damage caused by leukocyte activation. In muscle this effect of HBO is mediated by inhibiting synthesis of guanylate cyclase (cGMP) and subsequent leukocyte β−2integr independent adhesion.[119] This adhesion of leukocytes to vessel walls initiates the reperfusion injury inflammatory cascade.[120] In cardiac muscle the action of leukocytes is thought to be largely responsible for the reperfusion injury of myocardial infarction.[121] When the activation of leukocytes is blocked, they do not adhere to the β−2integrin receptor on the surface of vascular endothelium and reperfusion injury is prevented.[122] HBO acts to prevent this activation and adhesion.[123] In addition to the above mechanisms the primary reason for administration of HBO is the oxygenation of poorly vascularized tissue – a situation present in at least a small way in nearly every wound. In addition to the provision of tissue oxygenation levels many times the normal level, oxygen is a potent vasoconstrictor and is capable of reducing the edema in injured tissue, facilitating blood flow and further oxygenation. Thus, for those battle casualties who are undergoing additional surgeries during the time of their treatment under NBIRR, they can be expected to heal faster with less scar tissue formation. If there are a sufficient number of these cases, we will tag them in the database for additional analysis.

HBOT's mechanism is affected through the pharmacological properties of pressure-induced

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[118] Ibid.
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dissolution of large amounts of molecular oxygen in plasma according to Henry's Law.[124] Unfortunately, despite the plethora of studies on basic HBOT effects in acute CNS in animals and humans and chronic non-CNS pathophysiology in humans there are no studies on chronic CNS pathophysiology in animals beyond the open focal cortical contusion model.[125] The best-known drug effects of HBOT are those associated with its use in the acute treatment of decompression illness (DCI), namely bubble compression, bubble dissolution, and the alleviation of ischemia and hypoxia[126]. In addition, Harch and colleagues have previously observed potential effects in chronic injury while treating Gulf of Mexico divers with acute DCI[127]. Divers with weeks to months delay to recompression responded similarly to more acute cases. Moreover, repetitive HBOT (tailing treatment) in these late presentation divers resulted in the same effect as repetitive HBOT in acute cases. Lastly, clinically stable divers with residual brain injury from DCI had a significant positive response to a lower pressure protocol of HBOT[128] that had been previously applied to patients with chronic stroke[129] and multiple sclerosis[130]. In the past 20 years HBOT 1.5 (less than 2 ATA) has been applied to patients with chronic brain injury of a variety of etiologies, including coma[131], TBI[132], natural gas/carbon monoxide poisoning[133], global ischemia[134], near-drowning[135], cerebral palsy (CP)[136], and [CP, TBI, global

[124] U.S. Navy Diving Manual, Volume 1. NAVSEA 0994-LP-001-9010, Revision 1, 1 June 1985. Sec. 2.4.6.1, p2-20. Best Publishing Co., Flagstaff, AZ.

[125] Harch PG, Kriedt CL, Weisand MP, Van Meter KW, Sutherland RJ. Low pressure hyperbaric oxygen therapy (HBOT 1.5) induces cerebrovascular changes and improves cognitive function in a rat traumatic brain injury (TBI) model. Undersea Hyper Med 2001; 28 Suppl :28.

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[133] Neubauer RA. Severe natural gas poisoning successfully treated with hyperbaric oxygen – 2 years later. Neurotoxicology and Occupational Neurology, 1990;10; Harch PG, Van Meter KW, Gottlieb SF, Staab P. HMPAO SPECT brain imaging of acute CO poisoning and delayed neuropsychological sequelae (DNSS). Undersea & Hyperbaric Medicine, 1994; 21 (Suppl): 15.

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ischemia/anoxia, stroke, Lyme's Disease, and "other"][137]. The majority of these studies have reported positive results; however, only two of them are randomized controlled trials.

PREVIOUS & PRESENT STUDIES

HBOT 1.5, Chronic Brain Decompression Illness, and SPECT

The clinical experience with three groups of divers treated with HBOT 1.5 and who had recovery from DCI was confusing and contrary to the dogma in diving medicine which presumed that separated inert gas was the sole pathological target of hyperbaric recompression. The finding of delayed treatment benefit prompted a review of the U.S. Navy animal literature on brain decompression illness, which revealed that the majority of small bubbles directly presented to the brain via carotid injection passed through the brain vasculature within three to five minutes[138]. The bubble passage resulted in mechanical endothelial injury and a secondary inflammatory cascade characterized by reperfusion injury, ischemia[139], hypoxia, edema[140] and wbc infiltration.[141] All of this literature, an additional study on acute treatment of DCI[142], and our findings led to the supposition that much of the benefits of treatment of acute human cerebral DCI (beyond the first hour of injury, the timeframe and experience upon which U.S. Navy treatment was based) was not a consequence of treating separated gas, but of addressing residual effects of reperfusion injury and ischemia[143]. More importantly, we hypothesized that the tailing treatment of both acute and delayed presentation cases and retreatment of cases with chronic neuro-

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In: Abstracts VII Int Cong HBO Medicine, Moscow September 2-6, 1981:368; Montgomery D, Goldberg J, Amar M, Lacroix V, Le Comte J, Lambert J, Vanasse M, Marois P Effects of hyperbaric oxygen therapy on children with spastic diplegic cerebral palsy: a pilot project. Undersea Hyperbaric Medicine 1999;26(4):235-242; Collet JP, Vanasse M, Marois P, Amar M, Goldberg J, Lambert J, Lassonde M, Hardy P, Fortin J, Tremblay SD, Montgomery D, Lacroix J, Robinson A, Majnemer A, and the HBO–CP Research Group Hyperbaric oxygen for children with cerebral palsy: a randomized multicentre trial. Lancet, 2001;357:582-586; Multiple Studies. In: The 2nd International Symposium on Hyperbaric Oxygenation and the Brain Injured Child. Best Publishing Co, Flagstaff, AZ, 2002; Waalkes P, Fitzpatrick DT, Stankus S, Topolski R Adjunctive HBO treatment of children with cerebral anoxic injury. U.S. Army Medical Journal April-June 2002:13-21; Golden ZL, Neubauer R, Golden CJ, Greene L, Marsh J, Mleko A Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy. Intern. J. Neuroscience 2002;112:119-131; Hardy P, Collet JP, Goldberg J, Ducruet T, Vanasse M, Lambert J, Marois P, Amar M, Montgomery DL, LeComte J, Johnston KM, Lassonde M Neuropsychological effects of hyperbaric oxygen therapy in cerebral palsy. Dev Med Child Neurol 2002;44:436-446.

[137] Golden ZL, Neubauer R, Golden CJ, Greene L, Marsh J, Mleko A Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy. Intern. J. Neuroscience 2002;112:119-131.

[138] Gorman DF, Browning DM. Cerebral vasoreactivity and arterial gas embolism. Undersea Biomed Res, 1986 Sept:13(3):317-35; Helps, et al (1990): Increasing doses of intracarotid air and cerebral blood flow in rabbits. Stroke 1990; 21: 1340-1345; Cockett ATK, Zehl DN, Hanley J, Adey WR, Roberts AP. Effects of emboli on the neurocirculatory system in decompression sickness. In: Trapp WG, Banister EW, Davison AJ, Trapp PA, editors. Proceedings of the 5th International Hyperbaric Congress, Vol. II, 1973. Simon Fraser University, Burnaby 2, B.C., Canada, 1974.

[139] Harch PG, Gottlieb SF, Van Meter KW, Staab P. SPECT brain imaging in the diagnosis and treatment of type II decompression sickness. Undersea Hyper Med, 1992;19(Suppl):42; Harch PG, Van Meter KW, Gottlieb SF, Staab P. 29. Harch PG, et al. Delayed treatment of type II DCS: the importance of HBOT 1.5 and HMPAO SPECT brain imaging in its diagnosis and treatment. Undersea Hyper Med, 1993;20 (Suppl):51; Harch PG, Van Meter KW, Gottlieb SF, Staab P. The effect of HBOT tailing treatment on neurological residual and SPECT brain images in type II (cerebral) DCI/CAGE. Undersea and Hyper Med, 1994;21(Suppl):22-23; Harch PG. Late treatment of decompression illness and use of SPECT brain imaging. In: Moon RE, Sheffield PE, editors. Treatment of decompression illness. 45th Workshop of the Undersea and Hyperbaric Medical Society. Kensington (MD) UHMS, 1995, 203-42; Barratt DM, Harch PG, Van Meter K. Decompression illness in divers: A review of the literature. Neurologist 2002; 8:186-202.

[140] Hills JA, James PB (1991): Microbubble damage to the blood brain barrier: relevance to DCS. *UBR* 1991; 18(2): 111-116.

[141] Dutka AJ, Kochanek PM, Hallenbeck JM (1989): Influence of granulocytopenia on canine cerebral ischemia induced by air embolism. Stroke 1989 March;20(3):390-5; Helps SC, Gorman DF (1991): Air embolism of the brain in rabbits pretreated with mechlorethamine. Stroke 1991 March;22(3):351-4.

[142] Thalmann ED (1990) Principles of U.S. navy recompression treatments for decompression sickness. In: Diving Accident Management, 41st Undersea and Hyperbaric Medical Society Workshop. *Undersea and Hyperbaric Medical Society* publication 78 (DIVACC), 12/1/90:194-221.

[143] Harch PG. Late treatment of decompression illness and use of SPECT brain imaging. In: Moon RE, Sheffield PE, editors. Treatment of decompression illness. 45th Workshop of the Undersea and Hyperbaric Medical Society. Kensington (MD) UHMS, 1995, 203-42.

cognitive residual was primarily altering the sequelae of subacute/chronic ischemic brain injury[144] and treating the microscopic residual effects of mechanical bubble injury and inflammation.[145]

Application of HBOT 1.5 and SPECT to Chronic TBI

In 1990 the HBOT 1.5 protocol used in the chronic divers was applied to a small IRB-approved study of two boxers with *dementia pugulistica* who experienced transient improvement in dizziness, and mild sustained improvements in behavior, affect, and psychometric testing, respectively (unpublished data). These encouraging results led to a study of patients with a wide spectrum of chronic brain disorders who were evaluated and treated with HBOT 1.5. The study tested whether 40-treatment blocks of HBOT 1.5 could improve symptoms, abnormal physical exam findings, performance on cognitive tests, and rCBF deficits seen on SPECT brain imaging in patients with a minimum one-year-old brain injury. In addition, the study tested whether the rCBF response to a single HBOT treatment would identify perfusion deficits that improved after the single HBOT and thus could predict symptom/exam/ cognitive/SPECT improve-ment after a 40 HBOT treatment course, perhaps in concert with the "Idling Neuron" hypothesis.[146] In other words, the study attempted to see if SPECT identified injured areas of brain that could be rehabilitated with repetitive HBOT (SPECT was used as a surrogate biomarker and indexing tool because of previous success with this in a stroke case[147] and with divers[148]).

While a number of CNS disorders were studied[149], the experience in mild to moderate chronic TBI was nearly as successful as the treatment of the divers[150]. Further, the responsive areas of injured brain could be identified on SPECT during the acute rCBF response test (see Figure 1 below). We speculated that the similarity of responsiveness to HBOT 1.5 in the two groups was due to: 1) the presence of microscopic ischemic foci in

[144] Harch PG, Gottlieb SF, Van Meter KW, Staab P. SPECT brain imaging in the diagnosis and treatment of type II decompression sickness. Undersea Hyper Med, 1992;19(Suppl):42; Harch PG, Van Meter KW, Gottlieb SF, Staab P. 29. Harch PG, et al. Delayed treatment of type II DCS: the importance of HBOT 1.5 and HMPAO SPECT brain imaging in its diagnosis and treatment. Undersea Hyper Med, 1993;20 (Suppl):51; Harch PG, Van Meter KW, Gottlieb SF, Staab P. The effect of HBOT tailing treatment on neurological residual and SPECT brain images in type II (cerebral) DCI/CAGE. Undersea and Hyper Med, 1994;21(Suppl):22-23; Harch PG. Late treatment of decompression illness and use of SPECT brain imaging. In: Moon RE, Sheffield PE, editors. Treatment of decompression illness. 45th Workshop of the Undersea and Hyperbaric Medical Society. Kensington (MD) UHMS, 1995, 203-42; Barratt DM, Harch PG, Van Meter K. Decompression illness in divers: A review of the literature. Neurologist 2002; 8:186-202.

[145] Palmer AC, Calder IM, Yates PO. Cerebral vasculopathy in divers. Neuropath and Appl Neurobiol, 1992;18:113-124.

[146] Neubauer RA, Gottlieb SF, Kagan RL: (1990): Enhancing "idling" neurons. *Lancet* 1990 Mar 3;335:542.

[147] Ibid.

[148] Harch PG, Gottlieb SF, Van Meter KW, Staab P. SPECT brain imaging in the diagnosis and treatment of type II decompression sickness. Undersea Hyper Med, 1992;19(Suppl):42.

[149] Harch PG. Late treatment of decompression illness and use of SPECT brain imaging. In Treatment of Decompression Illness, 45th Workshop of the Undersea and Hyperbaric Medical Society (eds RE Moon, PJ Sheffield). UHMS, Kensington, 1996, 203-242.; Harch PG, Van Meter KW, Gottlieb SF, Staab P. HMPAO spect brain imaging of acute CO poisoning and delayed neuropsychological sequelae (DNSS). Undersea & Hyperbaric Medicine, 1994;21(Suppl):15.; Harch PG, Van Meter KW, Gottlieb SF, Staab P. The effect of HBOT tailing treatment on neurological residual and SPECT brain images in type II (cerebral) DCI/CAGE. Undersea & Hyperbaric Medicine, 1994;21(Suppl):22-23.; Harch PG, Gottlieb SF, Van Meter KW, Staab P. HMPAO SPECT brain imaging and low pressure HBOT in the diagnosis and treatment of chronic traumatic, ischemic, hypoxic and anoxic encephalopathies. Undersea & Hyperbaric Medicine, 1994; 21(Suppl):30.; Paul G. Harch, Keith W. Van Meter, Sheldon F. Gottlieb, Paul Staab. Delayed treatment of type II DCS: the importance of low pressure HBOT and HMPAO SPECT brain imaging in its diagnosis and treatment. Undersea & Hyperbaric Medicine, 20(Suppl):51, 1993.; Paul G. Harch, Sheldon F. Gottlieb, Keith Van Meter, Paul K. Staab. SPECT brain imaging in the diagnosis and treatment of type II decompression sickness. Undersea Hyper Med, 1992;19(Suppl):42.

[150] Harch PG, Van Meter KW, Gottlieb SF, Staab P. The effect of HBOT tailing treatment on neurological residual and SPECT brain images in type II (cerebral) DCI/CAGE. Undersea and Hyper Med, 1994;21(Suppl):22-23; Harch PG. Late treatment of decompression illness and use of SPECT brain imaging. In: Moon RE, Sheffield PE, editors. Treatment of decompression illness. 45th Workshop of the Undersea and Hyperbaric Medical Society. Kensington (MD) UHMS, 1995, 203-42.

both conditions (primary white matter vascular injury with secondary ischemia in decompression sickness[151], direct white matter injury[152] with secondary ischemia in mild TBI, 2) the small size of the perfusion gradient wounds in both conditions (heterogeneous pattern on SPECT[153]), and 3) the predominance of ischemic relative to infarcted tissue (normal anatomic imaging in both DCS and mild TBI). Mechanisms of action, however, were completely unknown.

Animal Confirmation of HBOT 1.5 in Chronic TBI

In 1995 duplication of the human HBOT/TBI experience and demonstration of the known angiogenic effect of HBOT in chronic wounds was sought in animals. Harch, and Kriedt and Sutherland (Univ. of New Mexico) applied the human protocol used in divers and TBI patients above to a group of 12 rats in a controlled study of chronic traumatic brain injury[154]. This open focal cortical contusion model[155] causes a cortical infarct and a contusion to the underlying hippocampus that partially mimics the acceleration/deceleration injury of blunt head trauma. The hippocampal injury results in a deficit in spatial memory and microscopic anatomic tissue injury[156] which are both characteristic of and similar to mild TBI. Fifteen days after injury the infarct to the cortex is complete and the injury to both cortex and hippocampus is considered chronic[157]. The human HBOT 1.5 protocol (above preliminary studies) applied forty-five days post injury produced statistically significant relative increases in hippocampal blood vessel density that correlated with simultaneous improvement in learning/spatial memory (hippocampal function), in essence a partial reversal of the traumatic hippocampal injury. The increase in blood vessel density was consistent with the known angiogenic effect of HBOT in chronic shallow perfusion gradient wounds cited above[158].

The pattern of relative increase in vessel density to injured hypometabolic rat brain tissue corresponded closely to the pattern of improvement noted on SPECT brain imaging in the above cases where the overall regional rCBF progressed from a heterogeneous pattern to a homogeneous pattern (See enclosed Cases #1 and 2 below). To exclude the possibility

[151] Palmer AC, Calder IM, Yates PO. Cerebral vasculopathy in divers. Neuropath and Appl Neurobiol, 1992;18:113-124.
[152] Povlishock JT, Christman CW. The Pathobiology of Traumatically Induced Axonal Injury in Animals and Humans: A Review of Current Thoughts. J of Neurotrauma, 1995;12(4):555-564; Oppenheimer DR. Microscopic lesions in the brain following head injury. J Neurol Neurosurg Psychiat, 1968;31:299-306.
[153] Harch PG, Gottlieb SF, Van Meter KW, Staab P. SPECT brain imaging in the diagnosis and treatment of type II decompression sickness. Undersea Hyper Med, 1992;19(Suppl):42; Harch PG, Van Meter KW, Gottlieb SF, Staab P. 29. Harch PG, et al. Delayed treatment of type II DCS: the importance of HBOT 1.5 and HMPAO SPECT brain imaging in its diagnosis and treatment. Undersea Hyper Med, 1993;20 (Suppl):51; Harch PG, Van Meter KW, Gottlieb SF, Staab P. The effect of HBOT tailing treatment on neurological residual and SPECT brain images in type II (cerebral) DCI/CAGE. Undersea and Hyper Med, 1994;21(Suppl):22-23; Harch PG. Late treatment of decompression illness and use of SPECT brain imaging. In: Moon RE, Sheffield PE, editors. Treatment of decompression illness. 45th Workshop of the Undersea and Hyperbaric Medical Society. Kensington (MD) UHMS, 1995, 203-42; Barratt DM, Harch PG, Van Meter K. Decompression illness in divers: A review of the literature. Neurologist 2002; 8:186-202.
[154] Harch PG, Kriedt CL, Weisend MP, Van Meter KW, Sutherland RJ. Low pressure hyperbaric oxygen therapy induces cerebrovascular changes and improves complex learning/memory in a rat open head bonk chronic brain contusion model. Undersea and Hyperbaric Med, 1996;23(Suppl):48.
[155] Feeney DM, Boyeson MG, Linn RT, Murray HM, Dail WG: Responses to cortical injury: I. Methodology and local effects of contusions in the rat. Brain Res. 1981 Apr 27;211(1):67-77.
[156] Ibid.
[157] Ibid.
[158] Marx RE, Ames JR. The use of Hyperbaric Oxygen Therapy in Bony Reconstruction of the Irradiated and Tissue-deficient Patient. J Oral MaxilloFac Surg, 1982;40:412-20; Marx RE. Osteoradionecrosis of the Jaws: Review and Update. HBO Review, 1984;5(2):78-126.

that these findings were a Type II error, the experiment was replicated with 60 rats in 2001; the results were statistically stronger[159] (manuscript in process). To our knowledge this was the first ever demonstration of improvement in chronic animal brain injury of any etiology. More importantly, however, it reaffirmed the case series experience noted above in humans with TBI, suggested a generic effect on common microscopic tissue pathology and shallow perfusion gradient wounds in divers and mild TBI patients, demonstrated the known trophic effect of HBOT in chronic wounds, angiogenesis, and argued very strongly that the improvements seen in both the animals and humans could be extended to humans in a controlled trial. The results of this study are shown in the two bar graphs.

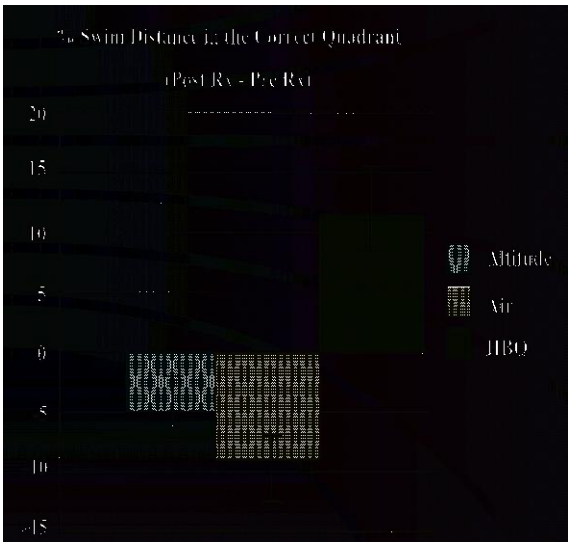

Figure: Improved Spatial Learning. Blue are altitude control rats (5,595 feet - Albuquerque), Yellow are s ham air dive rats at sea level, and Green are sea level HBOT rats. Bar graph denotes percent swim distance in the correct quadrant on the Morris Water Task (Spatial Learning Function).

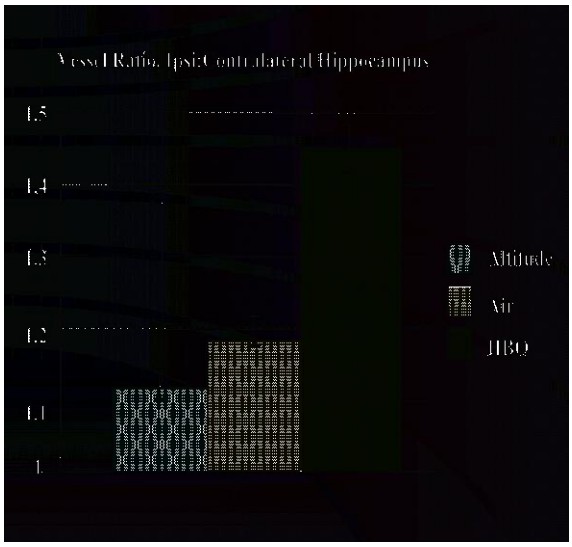

Figure: Blood vessel density ratio, ipsilateral to contralateral contused hippocampus. Color code is same as opposite figure.

[159]Harch PG, Kriedt CL, Weisand MP, Van Meter KW, Sutherland RJ. Low pressure hyperbaric oxygen therapy (LPHBOT) induces cerebrovascular changes and improves cognitive function in a rat traumatic brain injury (TBI) model. Undersea Hyper Med 2001; 28 Suppl :28.

WMS-R Delayed Memory Scale		
Patient	pre-HBO	post-HBO
A. T.	104	115
S. H.	99	140
C. R.	90	86
R. R.	127	124

Wechsler Adult Intelligence Scale I.Q. Changes with HBO Therapy			
Verbal		Performance	
before	after	before	after
99	115	97	107
127	128	148	140
86	90	73	79
113	116	104	118

Cumulative Experience of HBOT 1.5 and SPECT in Chronic Human TBI

Over the past 16+ years we have treated approximately 60 patients with varying severities of chronic (greater than one year post injury) traumatic brain injury in a case series format using each patient as his/her own control. The subjects have undergone the acute rCBF response measure (see Figure 1. This is directly below and is a sample of the scans from Case #2) as a provocative test of capacity to respond to HBOT, blocks of 40 HBOT 1.5 treatments, and a variety of outcome measures, including symptoms and signs, psychometric testing, and follow up SPECT brain imaging. In the context of an unfunded pilot study, only SPECT imaging was performed on all patients since the predictive ability of SPECT was one of the primary hypotheses of the study. Preliminary analyses indicate that the great majority of patients responded positively with lasting symptomatic, cognitive, and rCBF improvements. Qualitative changes (visual interpretation) on SPECT have been substantial and the acute rCBF response test predicted improvement of perfusion deficits on the second scan and the final scan after a series of HBOT's. (See attached Cases #1 and 2.) In most of these cases the effect of HBOT is a smoothing of the trauma induced heterogeneous pattern of flow to the more normal homogeneous pattern of brain blood flow. Three-dimensional surface reconstructions have often dramatically recorded the improvements in flow to damaged areas and reflected the slice image pattern change from a coarse heterogeneous pattern to a smoother pattern (See Cases #1 and 2). Patients with both negative and positive anatomic imaging, indicating an effect on both microscopic and macroscopic tissue injury, exhibited the pattern of change. The SPECT brain imaging improvements were the most consistent and seem to be independent of etiology or severity of TBI[160]. Although

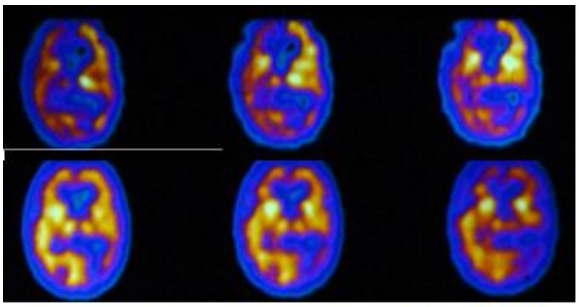

Figure 1. Case A pre (top) and post (bottom) HBOT

[160] Harch PG, Van Meter KW, Gottlieb SF, Staab P. HMPAO SPECT brain imaging and low pressure HBOT in the diagnosis and treatment of chronic traumatic, ischemic, hypoxic and anoxic encephalopathies. Undersea and Hyperbaric Medicine, 1994;21(Suppl):30; Harch PG, Van Meter KW, Neubauer RA, Gottlieb SF. Use of HMPAO SPECT for assessment of response to HBO in ischemic/hypoxic encephalopathies. In: Jain KK editor. Textbook of Hyperbaric Medicine, Appendix, 2nd ed, 480-491. Seattle (WA): Hogrefe &Huber Pubs., 1996; Harch PG, Neubauer RA (1999) Hyperbaric oxygen therapy in global cerebral ischemia/ anoxia and coma. In Jain KK (ed) *Textbook of Hyperbaric Medicine, 3rd Revised Edition, Chapter 18.* Hogrefe & Huber Publishers, Seattle WA 1999: 319-345.

symptomatic improvements were not recorded using standardized questionnaires in this pilot study, most of the patients with mild TBI were able to return to school, work, and/or increase their post-injury level of function and performance. Psychometric testing or SAT scores pre- and post-HBOT measured the cognitive gains in the mild TBI patients. Some of these gains were significant (Case #1's delayed memory scores are shown below. Case #2's improvement on the Rey-Osterrieth Complex Figure is shown in Figure 2). One 17 year old individual who was 2 years post severe TBI (GCS=7) obtained pre-HBOT SAT scores (percentiles) of 8 Verbal and 15 Math. Repeat testing one month later improved to 14 Verbal and 22 Math, likely an improvement due to practice. Repeat SAT scores after a course of HBOT (five months post first SAT testing) were 14 Verbal and 49 Math. Pre/Post HBOT Wechsler delayed memory scores of four other individuals are tabulated below; they were used in the power analysis for this study. Their I.Q. changes are also provided.

Case 1: Patient is a 48-year-old female who was involved in a motor vehicle accident (MVA) that resulted in LOC of less than one minute. GCS in the ER was 14 for 16 hours. Repetitive acute CT imaging was negative. Two years later the patient was evaluated for short-term memory dysfunction, problems with attention and concentration, and inability to organize her thoughts that prevented return to work. The patient underwent SPECT then single HBOT the following day with repeat SPECT as shown in Figures 1.A. Display orientation is standard CT convention with the patient's right on the reader's left. Transverse slices begin at the vertex of the head in the left upper corner and proceed to the base of the brain in the right lower corner of each study. Baseline SPECT is on the left. Color map is bright white yellow, yellow, orange, purple, blue, and black from highest to lowest blood flow. Note the diffusely coarse heterogeneous pattern on the baseline scan which "smooths" modestly to a more normal homogeneous pattern of blood flow on the after HBOT scan. The patient commenced a course of 40 1.5 ATA/60 minute HBOT's over the next 30 days and experienced improvement in her cognitive deficits that facilitated return to work. Repeat SPECT obtained three weeks post the 40th HBOT, shown in Figure 1.B on the left with the first SPECT on the right, duplicates the homogeneous smoothing of the second SPECT. The global improved blood flow is consistent with the patient's symptomatic and psychometric test score (see above text box) improvements. Three-dimensional surface reconstructions of the three scans are shown in chronological order in Figures 1.C, D, and E.

Case 2: Patient is a 19-year-old male who was injured in a severe MVA two and one half years previously. GCS post prolonged extrication in sub-zero temperature was 6-7. Following rehabilitation the patient was left with inappropriate social behavior, significant cognitive deficits, perseveration, and required constant supervision. The patient was evaluated with the sequence of SPECT and next day HBOT with repeat SPECT as shown in Figures 2.A and B. Note the significant reductions in right frontal, temporal, thalamic, and right and left superior basal ganglia blood flow, infarct to the left parietal/occipital area, and cerebellar diaschisis. The patient underwent a course of eighty 1.5 ATA/90 HBOT's in the next six months (treatment broken by hurricane) and experienced improvement in social behavior, cognitive function, and perseveration. His improved function facilitated advance to assisted living in a group home and part-time employment. Repeat SPECT

after the 80th HBOT is shown in Figures 2.C and D on the right side, opposite the baseline scan on the left. Note the resolution of cerebellar diaschisis and improvement in brain blood flow to nearly all deficit areas, especially the right frontal and temporal lobes. Simultaneously, the patient showed improvement in pre/post psychometric testing shown most convincingly on the Rey-Osterrieth Complex Figure Drawing in Figures 2. E, F, G, H, I, and J. E, F, and G are the pre-HBOT "copy", "immediate recall", and "delayed recall" on the top row and H, I, and J are the post-HBO identical sequence on the bottom row. Note the maintenance of size (slight increase) and detail of the post-HBOT test.

Demonstration of HBOT 1.5 and SPECT in other Neuropathology

A quantitative analysis of rCBF images was recently conducted (by MDD at UT Southwestern) in data from our pediatric brain injured patients treated in the large pilot project described above. A voxel-wise SPM (Statistical Parametric Mapping) analysis of rCBF (SPECT) in 18 cerebral palsy, autistic, and air embolism patients was conducted. Scans for pre HBOT, after one HBOT, and after 80 HBOT's were averaged and compared longitudinally. Among other findings, this analysis showed a significant rCBF response to a single HBOT relative to the pretreatment state (see Figure 2), manifested as increased rCBF in medial temporal lobe and visual cortex, and decreased anterior cingulate rCBF. In addition, these rCBF changes were nearly identical to the group changes seen on final SPECT after a course of HBOT 1.5. While these data are representative of some of the analysis techniques to be employed, our primary focus will be on within-subject (still assessed with SPM) rather than group effects since the large inter-subject variance in pathology limits interpretation of group results. However, we are also interested in common consequences of TBI and will conduct group analyses such as illustrated in Figure 2 as well.

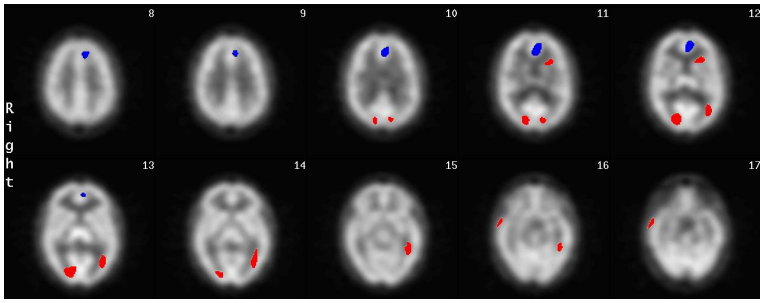

Figure 2. Acute response to HBOT: areas of increased flow in red and decreased flow in blue.

Additional Evidence of HBOT 1.5 in Chronic TBI

The CP findings are also consistent with a case report of HBOT 1.5 and SPECT brain imaging in the treatment of chronic TBI[161]-(symptomatic gains, no psychometric testing) and our controlled study of HBOT, psychometric testing, and SPECT brain imaging conducted at the Transitional Learning Community and the University of Texas Medical Branch, Galveston[162]. In this study the patients improved symptomatically, on SPECT, and showed a trend of improvement on psychometric testing. The sequence of scan/dive/scan did not yield positive results, but the protocol was performed differently than that described above with the second scan occurring 24 hours after the first HBOT. In addition, a group of normal patients subjected to HBOT and SPECT showed no significant SPECT changes.

[161] Neubauer RA, Gottlieb SF, Pevsner NH. Hyperbaric Oxygen for Treatment of Closed Head Injury. Southern Medical Journal, 1994;87(9):933-936

[162] Barrett KF, Masel BE, Harch PG, et al. Cerebral blood flow changes and cognitive improvement in chronic stable traumatic brain injuries treated with hyperbaric oxygen therapy. Neurol, April, 1998 (Suppl):A178-A179.

CRITERIA FOR SUBJECT SELECTION

One thousand subjects will be recruited for this longitudinal observational study.

The number of subjects at each site will depend upon the local population of injured, the capacity of the site to provide treatment, and reimbursement availability.

Subjects will be 18-65 years old and have been diagnosed with mild or moderate (but not severe) TBI or TBI/PTSD or PTSD by either the military (any etiology) or civilian neurologists or neuropsychologists. This diagnosis will especially include war veterans who have received the ANAM test pre- and post-deployment and had a significant decrease in their neuropsychological test scores.

Gender Restrictions

There will be no gender restrictions. However, it is anticipated that the cohort will consist mostly of males, due to the nature of the injury and the preponderance of men in the military serving in combat arms units.

Racial & Ethnic Origin

The demographics of the study subjects will likely mirror the demographics of the military since the study will likely have a high proportion of military TBI subjects. The military has a high minority representation. No attempt will be made to limit minority involvement in the study nor will attempt to target particular minorities for enrollment.

Subjects will be enrolled who meet study criteria regardless of etiology of injury, race, or other discriminatory factors, including gender. Though there has been a preponderance of injury in the combat arms units, where nearly 100% of veterans report at least one concussive injury, about 50% of the Combat Support and Combat Service Support (like transportation and water purification and military police) report having had at least one concussive blast. This is expected to create a large cohort of female patients in the larger study, especially including the National Guard, because of the make up of those units. We expect the study to include more men than women, but there should be a sufficient number of women to gain accurate results. There has been no appreciable difference between the sexes in civilian treatment of TBI with HBOT 1.5.

Inclusion Criteria

a. Any 18-65 year-old patient with mild-moderate TBI or PTSD. (If a military injury, subject may be active duty or a veteran. Subjects with PTSD only will be enrolled because of military medicine's difficulty in distinguishing between these patients. Also, DoD medical or Veteran's Administration disability boards will give a PTSD designation before a TBI designation because the disability rating payment scale is less for PTSD than for TBI.)
b. Have demonstrated a >20% decrement (compared to pre-deployment baseline) in ANAM composite score or specific sub-score with regard to "simple reaction time" and/or "procedural reaction time".
c. Have a diagnosis of TBI, chronic TBI/PCS or TBI/PCS/PTSD or PTSD made by a military (military etiology of blast injury) or civilian neurologist (and neuropsychologist).
d. Negative pregnancy test in females.

e. Less than 90% on the Percent Back to Normal Rating Scale. (If patient is considered 100% normal before TBI, patient should be less than 90% normal for entry into the study).

Exclusion Criteria

a. Pulmonary disease that precludes HBOT (e.g., asthma unresponsive to medication, bullous emphysema).
b. Unstable medical conditions that are contraindicated in HBOT (e.g. severe congestive heart failure or heart failure requiring hospital emergency evaluation or admission in the previous year).
c. Severe confinement anxiety (e.g., patients who require anesthesia conscious sedation for MRI or who cannot go in elevators).
d. Pregnancy.
e. Other pre-TBI neurological diagnoses.(seizure disorders, multiple sclerosis, Parkinson's, Lyme, etc.)
f. Participation in another experimental trial with active intervention.
h. High probability of inability to complete the experimental protocol (e.g. terminal condition).
i. Past or current history of mental retardation unless diagnosed post TBI (baseline IQ ≤ 70).
j. Pre- or post-TBI history of systemic illness with impact on central nervous system. (Principal Investigator in consultation with study sponsor Medical Officer will make the ultimate decision).
k. Any pre-existing chronic infection not related to battlefield injuries or government service.

Vulnerable Subjects

All subjects will be legally capable of consenting. No subjects who need 3rd party consent will be enrolled in the NBIRR study.

Military - special care and precautions: The subjects will have to voluntarily contact NBIRR participating sites or respond to a recruitment outreach outside of the command. (Once the present NBIRR IRB-protocol is approved, and if the protocol is to be used at a military site, Memorandum of Agreement procedures will be followed to comply with military IRB requirements.)

Homeless - special care and precautions: All state and local laws will be followed as the NBIRR team works with federal, state and local homeless programs.

METHODS AND PROCEDURES

After a patient inquiry is received the office staff, under the supervision of the PI, will do the initial qualifications assessment and then as appropriate, will schedule the patient for a medical interview and examination. After medical examination and final qualification, they will be scheduled within one week to undergo baseline testing (characterization of initial status) and will begin the therapy within two weeks of formal entry into the study.

The subject's baseline will be ascertained by various means. Some of these characterizations will be specific to those patients with a military etiology. For all subjects with a head injury, the subject will be asked to characterize the nature of the injury (time, date, place, circumstances, loss of consciousness, residual symptoms). For those with a blast injury, we will ascertain, for each exposure, the approximate time, place, distance from the blast, body orientation with regard to the blast, and frequency of exposure. We will determine if there was any loss of consciousness, medical characterization of same, time course of recovery, and residual symptoms.

In addition to above, for military etiology TBI, the patient's diagnosis according to the military physicians will be ascertained, along with any revision during treatment. Specific forms will be used to characterize the military exposure (see below).

Subjects will begin vitamin C, E, and multivitamin / multi-mineral supplementation for co-factor and antioxidant support prior to and throughout the period of HBO treatment. Since there is a general clinical concern regarding potential for toxicity from heavy metal exposure and many subjects will be on treatment for this based on a clinical recommendation, we will try to make this process consistent among the subject by recommending an appropriate nutritional supplement like "Modiflan", a kelp powder used to treat victims of Chernobyl or a form of solubilized pectin. There is no good evidence for the use of these vitamins, minerals or natural heavy metal binders in hyperbaric oxygen therapy and there is no accepted standard combination of treatments. However, the use of minimal supplementation for anti-oxidant effect has emerged as a standard of care in hyperbaric oxygen therapy. Similarly, heavy metal reduction may be important to maximize the effect of oxygen by reducing the blockage of oxygen utilization and minimizing neurological harm caused by heavy metals that could impede or otherwise confuse clinical response to HBOT.

Screening

To determine qualification for the study, patients will be questioned by the site investigator (or staff under direct supervision of the PI) using simple screening questions to determine qualification for the study, regarding hyperbaric oxygen therapy, absolute and relative contraindications, and other inclusion and exclusion criteria. Upon their initial medical evaluation, they will then be consented by the site PI and complete the Rivermead Head Injury Questionnaire, the Michigan Alcohol and Drug Screening Tests (MAST & DAST) to characterize the level of substance abuse, the PTSD checklist to identify and verify the presence or absence of PTSD in TBI subjects, the automated tests ANAM and CNSVS. Depending upon the special assets or capabilities at particular locations, some patients

may receive specialized neuropsych testing or imaging at the physician's direction. We will collect as part of the study data from other neuropsych testing or imaging.

All subjects will proceed to evaluation with the tests to be described below. Subjects will be urine drug tested prior to enrollment and tested for pregnancy (monthly) then will complete QOL questionnaires that are described below. They will undergo neurological exam and hyperbaric medicine exam by the PI. They will be asked if they have had recent pre-post deployment ANAMs, imaging or full neuropsychiatric testing - if so, these data will be collected.

Disability Rating Scale
The Disability Rating Scale is a well-characterized instrument that reliably reflects general outcome in moderate to severe TBI and has been shown to correlate with electrophysiological measures of brain injury. It will be used to exclude the severely disabled and track outcomes on the Level of Functioning and Employability Items, the two scales shown to be sensitive to change 2-5 years post TBI. Severe TBI may be submitted on a separate IRB protocol, as the measurement tests and exams are different.

Hyperbaric Medical Exam
This exam will be performed by the site PI. It will be another layer of screening of the subject for overall fit to the study as well as assessment of hyperbaric medicine exclusions. Patients will also be instructed in how to clear their ears during chamber pressurization.

Neurological Exam
The neurological exam will be performed by the PI. The patients will be questioned for previous neurological disease. Neurological exam will emphasize balance and gait, two functions that have been found to be abnormal on physical exam in patients with mild or moderate chronic TBI.

Then, subjects will begin to undergo HBOT sessions at 1.5 atmospheres absolute (ATA) for 60 minutes once daily, 5d/week. For persons who have to travel, a modified protocol of twice daily for the first two weeks and once per day thereafter six days per week may be followed to shorten the travel expenses.

Subjects will undergo automated testing (ANAM, and CNSVS) neuropsychiatric testing and complete forms needed for monitoring purposes upon enrollment. Those who wait more than 30 days before their first treatment will be retested immediately before their first treatment. Testing will be repeated after 20, 40, 60 and 80 hyperbaric treatments. If necessary, some tests may need to be repeated (i.e., ANAM) to stabilize the results from the learning effect.

At the conclusion of 40 HBOT's the subjects will complete the PBNRS. If the score is ≥ 90% the subjects will have a repeat automated psychometric test battery, QOL questionnaires, urine drug testing, and pregnancy testing.

If the PBNRS is < 90% the subjects will have another 20 HBOT's on a 5-6 HBOT/week schedule and repeat the automated tests. At clinical plateau by PBNRS or upon completion of 80 HBOT's, whichever should occur first, the subjects will repeat psychometric test battery, QoL questionnaires, PBNRS, urine drug test, and pregnancy test.

Six months after final HBOT subjects will be questioned by the PI (or by staff under supervision of PI) preferably in-person, or by phone or internet, regarding return to work or school and PBNRS. They will repeat the automated tests at this point.

Long-term follow up beyond this period will be enabled by phone and online automated testing; the patients will be requested to complete the automated tests every 6 months for up to 2 years.

Alcohol and Drug Abuse Assessment at Baseline and During Treatment / Michigan Alcohol and Drug Screening Tests

MAST & DAST are standardized measure of lifetime and current substance or alcohol abuse or dependence. Patients with severe scores will NOT be excluded from this study if they have past or current histories of significant substance/alcohol dependence or abuse. Higher severity scores are associated with more severe addictive symptoms on this measure, which could confound evaluation of any HBOT treatment effect. They will be tracked as such.

Psychometric Testing

To facilitate the scale of this study and to allow more frequent evaluation, it is necessary to rely primarily upon automated computerized internet-based neuropsychological tests and questionnaires.

Tests requiring a neuropsychologist can not be accomplished by automated methods, however, some measures of outcome are evaluable by CNSVS and ANAM, automated computerized tests.

Even though it is not a requirement of the study, the study results will be supported further by the fact that some fraction of subjects will also undergo more comprehensive neuropsychological assessment or imaging under the supervision of an appropriate health care professional. This data will be obtained and compiled for analysis using the data platform described below.

Neuropsychological tests and Quality of Life Questionnaires will be administered to each participant. The screening measures will be used to characterize the patients using diagnostic measures used by both the military and civilian diagnosticians.

The neuropsychological tests in this study are utilized for three purposes: 1) as pre-tests to measure each participant's baseline level of neuropsychological functioning including: intellectual functioning, memory, executive abilities, psychomotor speed and coordination, and psychosocial/adaptive functioning prior to HBOT, 2) as post-tests to measure the

effects of HBOT on the neuropsychological measures listed above, and 3) to measure constructs which serve as moderators for the effects of HBOT, including IQ, personality, and adaptive functioning. Although practice effects are observed on many tests, the automated tests being utilized all incorporate features to use alternative forms. Many other tests do not have large practice effects.

Since TBI consists of both focal and diffuse injuries, different patterns of cognitive, neurobehavioral, and adaptive functional impairments are found that contribute to heterogeneous courses and outcomes. In our experience HBOT has differential effects on these impairments that vary individually. To capture the heterogeneity of both the TBI and HBOT response, we will use multiple pre- and post-treatment neuro-behavioral and adaptive functional measures. All evaluations will be completed within the same week to permit relatively contemporaneous correlation analyses between pre- and post-neuropsychological, neurobehavioral, or adaptive functional outcome change scores.

Imaging
No imaging is done or required as part of this study. We will be careful not to interfere with the patient's medical care except to provide HBOT and automated neuropsychometric testing as part of this study.

If the patient has imaging (recommended by their physician outside of the study) after enrollment, we will make every effort to have the patient undergo the standard set of automated neuropsychological tests (ANAM and CNSVS) again within one week of any imaging studies.

Characterization of Subject's Military Experience and Etiology of Injury

PTSD Checklist PCL-M
The PCL is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. Respondents rate how much they were "bothered by that problem in the past month". Items are rated on a 5-point scale ranging from 1 ("not at all") to 5 ("extremely"). There are several versions of the PCL. The original PCL is the PCL-M (military). The PCL-M asks about problems in response to "stressful military experiences." The PCL-S (specific) asks about problems in relation to an identified "stressful experience." The PCL-C (civilian) is for civilians and is not focused on any one traumatic events. Instead it asks more generally about problems in relation to stressful experiences[163].

3Q DVBIC
The purpose of this screen is to identify service members who may need further evaluation for mild traumatic brain injury (MTBI). Screen should be used with service members who were injured during combat operations, training missions or other activities. The 3 Question DVBIC TBI Screening Tool, also called The Brief Traumatic Brain Injury Screen (BTBIS),

[163] (Weathers et al., 1993).

was validated in a small, initial study conducted with active duty service members who served in Iraq/Afghanistan between January 2004 and January 2005.[164]

Combat Exposure Scale (CES)

The Combat Exposure Scale (CES) is a 7-item self-report measure that assesses wartime stressors experienced by combatants. Items are rated on a 5-point frequency, 5-point duration, 4-point frequency or 4-point degree of loss scale. Respondents are asked to respond based on their exposure to various combat situations, such as firing rounds at the enemy and being on dangerous duty. The total CES score is calculated by using a sum of weighted scores, which can be classified into 1 of 5 categories of combat exposure ranging from "light" to "heavy." The CES was developed for easy administration and scoring; it is useful in both research and clinical settings.[165]

Documentation of TBI Cognitive Deficits

Rivermead Post Concussion Symptoms Questionnaire

The Rivermead Post Concussion Symptoms Questionnaire[23] measures the severity of PCS in TBI. It has been shown to reliably identify those patients with chronic cognitive deficits.

Individual item scores reflect the presence and severity of post concussive symptoms. Post concussive
symptoms, as measured by the RPQ, may arise for different reasons subsequent to (although not necessarily directly because of) a traumatic brain injury. The symptoms overlap with broader conditions, such as pain, fatigue and mental health conditions such as depression. The questionnaire can be repeated to monitor a patient's progress over time. There may be changes in the severity of symptoms, or the range of symptoms. Typical recovery is reflected in a reduction of symptoms and their severity within three months. Modified RPQ-3 and RPQ-13 scores will be calculated after the method of Eyres 2005.

Automated Neuropsychological Testing

ANAM

On May 28, 2008 The Assistant Secretary of Defense, Health Affairs office put out a memorandum directing all Services to begin implementing baseline pre-deployment Neurocognitive assessments for all Service members. All Services members are required to complete their pre-deployment Neurocognitive assessment within 12 months prior to deployment. This assessment is a mandatory requirement.

The purpose of this test is to establish a baseline in the event that the Service member becomes injured or is exposed to a traumatic brain injury. If the Service member is injured then they will take another test and the results would be compared to their original baseline

[164] (Schwab, K. A., Baker, G., Ivins, B., Sluss-Tiller, M., Lux, W., & Warden, D. (2006). The Brief Traumatic Brain Injury Screen (BTBIS): Investigating the validity of a self-report instrument for detecting traumatic brain injury (TBI) in troops returning from deployment in Afghanistan and Iraq. *Neurology, 66*(5)(Supp. 2), A235.
[165] (Keane, T., Fairbank, J., Caddell, J., Zimering, R., Taylor, K., & Mora, C., 1989)

to determine what would be the best course of treatment or care. This comparison will help determine the extent of the injury in a more efficient manner.

ANAM pre-deployment testing is not a diagnostic tool and is not used to determine if the Service Member is deployable or non-deployable.

ANAM is a proven computer-based tool designed to detect speed and accuracy of attention, memory, and thinking ability. It records a Service Member's performance through responses provided on a computer.

Since this test has a learning curve that occurs over about five testings, the first post-injury test is going to give us some measure of TBI and PTSD; however, we will have subjects perform at least three successive tests to plateau the subject's learning curve.[166]

(see also, Appendix II for more information regarding ANAM)

***CNS Vital Signs (six components described below)*:**
Verbal Memory (VBM) and Visual Memory (VIM) Tests: Vital Signs includes parallel tests of verbal memory (word list learning) and visual memory (figure learning). The tests are virtually identical, but one uses words as stimuli, the other, geometric shapes.

The verbal memory test (VBM) is an adaptation of the Rey Auditory Verbal Learning Test (Rey, 1964; Taylor, 1959). It is a recognition test, however, not a test of recall. In the CNS Vital Signs version, fifteen words are presented, one by one, on the screen. A new word is presented every two seconds. The subject is asked to remember these words. Then a list of thirty words is presented. The fifteen target words are mixed randomly among fifteen new words. When the subject recognizes a word from the original list, he or she presses the space bar. After this trial of thirty stimuli, the subject goes on to do the next six tests. At the end of the battery, about 20 min later, the fifteen target words appear again, mixed with 15 new non-target words.

The Visual Memory Test (VIM) in CNS Vital Signs is based on the Rey Visual Design Learning Test; the latter is, in turn, a parallel to the Rey Auditory Verbal Learning Test, using geometric figures rather than words, and requiring the subject to draw the figures from memory. In CNS Vital Signs, the visual memory test is just like the verbal memory test. Fifteen geometric figures are presented; the subject has to identify those figures nested among fifteen new figures. Then, after five more tests, there is a delayed recognition trial.

The VBM draws from a "reservoir" of 100 words selected from word-frequency tables. The VIM draws from a reservoir of 100 simple geometric designs. The scoring is correct hits and correct passes, immediate and delayed. Correct responses from VBM and VIM are

[166] http://www.armymedicine.army.mil/prr/anam.html)

summed to generate a composite memory or memory domain score. The highest score one can attain is 120; the lowest is 60. Scores below 60 suggest willful exaggeration.

Finger Tapping Test (FTT): The FTT is one of the most commonly used tests in neuropsychology, because of its simplicity and reliability, and because it generates relevant data about fine motor control, which is based on motor speed as well as kinesthetic and visual-motor ability (Mitrushina et al., 1999). It was one of the core tests of the Halstead–Reitan Battery, which dates to the 1940's, but similar tests were used by nineteenth century psychologists like Wundt, Galton and Cattell. The FTT is believed to be one of the most sensitive neuropsychological tests for determining brain impairment (Mitrushina et al., 1999).

In CNS Vital Signs, the FTT is a very simple test. Subjects are asked to press the Space Bar with their right index finger as many times as they can in ten seconds. They do this once for practice, and then there are three test trials. The test is repeated with the left hand. The score is the average number of taps, right and left.

Symbol Digit Coding (SDC): The Symbol Digit Modalities Test (SDMT) (Smith & Jones, 1982) is a variant of the Wechsler DSST, but the position of symbols and digits is reversed. The clinical and psychometric properties of the SDMT are similar to those of the DSST. Although the SDMT may be a "harder" test, and thus more sensitive to neurotoxicity, performance on the SDMT and the DSST are highly correlated (Lezak, 1994). Smith maintained that the SDMT was "usually the most sensitive (test) to the presence of acute or chronic 'organic' cerebral dysfunction" (Smith, 1982).

In the CNS Vital Signs SDC, the subject is given a training session to learn how to link numbers to digits. The test itself consists of serial presentations of screens, each of which contains a bank of eight symbols above and eight empty boxes below. The subject types in the number that corresponds to the symbol that is highlighted. Only the digits from 2 through 9 are used; this to avoid the confusion between "1" and "l" on the keyboard. The test lasts for 120s. The goal is to type in as many correct numbers as one can in 120s.

Neither the SDMT nor the DSST are suitable for repeated administration, because subjects are able to remember the code and thus accelerate their performance (Hindmarch, 1980). Modifications in the test are necessary if it is to be used repeatedly; for example, changing the code in a random way on successive administrations. The SDC in CNS Vital Signs draws from a reservoir of 32 symbols. Each time the test is administered, the program randomly chooses eight new symbols to match to the eight digits, allowing the test to be given serially.

The Stroop Test: There have been several versions of the Stroop test over the years. The modification adopted for CNS Vital Signs uses only four colors/color words (red, green, yellow, blue), and only one key is in play, the space bar. The test has three parts. In the first, the words RED, YELLOW, BLUE and GREEN (printed in black) appear at random on the screen, and the subject presses the space bar as soon as he or she sees the word. This generates a simple reaction time score.

In the second part, the words RED, YELLOW, BLUE and GREEN appear on the screen, printed in color. The subject is asked to press the space bar when the color of the word matches what the word says. This generates a complex reaction time score.

In the third part, the words RED, YELLOW, BLUE and GREEN appear on the screen, printed in color. The subject is asked to press the space bar when the color of the word does not match what the word says. This part also generates a complex reaction time score, called the "color-word reaction time". The color-word reaction time is, on average 120 ms longer than the complex reaction time generated in part two of the test (range, 78–188 ms) (the "Stroop effect").

The Shifting Attention Test (SAT): The Shifting Attention Test (SAT) measures the subject's ability to shift from one instruction set to another quickly and accurately. In the SAT test, subjects are instructed to match geometric objects either by shape or by color. Three figures appear on the screen, one on top and two on the bottom. The top figure is either a square or a circle. The bottom figures are a square and a circle. The figures are either red or blue; the colors are mixed randomly. The subject is asked to match one of the bottom figures to the top figure. The rules change at random. For one presentation, the rule is to match the figures by shape, for another, by color. This goes on for 90 s. The goal is to make as many correct matches as one can in the time allotted. The scores generated by the SAT are: correct matches, errors, and response time in milliseconds.

The Continuous Performance Test (CPT): The CPT is a measure of vigilance or sustained attention or attention over time (Rosvold & Delgado, 1956). It has been a popular test because of its robust relationship to psychiatric disorders. Poor performance on the CPT has been reported in ADHD (Epstein et al., 2001; Sykes et al., 1971), learning disabilities (Lindsay et al., 2001; McGee et al., 2000), patients with epilepsy (Mirksy & van Buren, 1965) and schizophrenics (Vadhan et al., 2001; Wohlberg &Kornetsky, 1973). It is sensitive to CNS dysfunction in general, and is not specific to any particular condition (Riccio & Reynolds, 2001).

The CPT is also sensitive, for better or worse, to the effects of various drugs. In ADHD children, performance on the CPT is reliably improved by stimulant medications (Barkley, 1977; Riccio et al., 2001). Alcohol consumption (Dougherty et al., 2000) adversely affects performance on the CPT, but nicotine tends to improve performance on the test (Levin et al., 2001). Certain anticonvulsant medications impair performance on the CPT (Hutt et al., 1968). The CPT in Vital Signs is a conventional version of the test, although it is shorter than some other versions. In the Vital Signs CPT, the subject is asked to respond to target stimulus "B" but not to any other letter. In 5 min, the test presents 200 letters. Forty of the stimuli are targets (the letter "B"), 160 are non-targets (other letters). The stimuli are presented at random, although the target stimulus is "blocked" so it appears eight times during each minute of the test.

Neurobehavioral & Quality of Life (QOL) Questionnaires

PRIME-MD Patient Health Questionnaire (PHQ)

Citation: The PHQ scales, including GAD-7, are free to use in clinical practice, research and education. The PHQ (and PHQ-9) are adapted from PRIME MD TODAY, developed by Drs. Robert L. Spitzer, Kurt Kroenke, and Janet B.W. Williams. Copyright ©1999 Pfizer Inc.

Purpose. The Patient Health Questionnaire (PHQ) is designed to facilitate the recognition and diagnosis of the most common mental disorders in primary care patients. For patients with a depressive disorder, a PHQ Depression Severity Index score can be calculated and repeated over time to monitor change.

Who Should Take the PHQ. Ideally, the PHQ should be used with all new patients, all patients who have not completed the questionnaire in the last year, and all patients suspected of having a mental disorder.

Making a Diagnosis. Since the questionnaire relies on patient self-report, definitive diagnoses must be verified by the clinician, taking into account how well the patient understood the questions in the questionnaire, as well as other relevant information from the patient, his or her family or other sources.

Interpreting the PHQ. To facilitate interpretation of patient responses, all clinically significant responses are found in the column farthest to the right. (The only exception is for suicidal ideation when diagnosing a depressive syndrome.) At the bottom of each page, beginning with “FOR OFFICE CODING”, in small type, are criteria for diagnostic judgments for summarizing the responses on that page. The names of the categories are abbreviated, e.g., Major Depressive Syndrome is Maj Dep Syn..

PHQ-9 Depression Severity Score. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of “not at all,” “several days,” “more than half the days,” and “nearly every day,” respectively. PHQ-9 total score for the nine items ranges from 0 to 27. In the above case, the PHQ-9 depression severity score is 16 (3 items scored 1, 2 items scored 2, and 3 items scored 3). Scores of 5, 10, 15, and 20 represent thresholds for mild, moderate, moderately severe and severe depression, respectively. Sensitivity to change has also been confirmed.

PHQ-15 Somatic Symptom Severity Score. This is calculated by assigning scores of 0, 1, and 2 to the response categories of “not at all”, “bothered a little”, and “bothered a lot”, for the 13 somatic symptoms. Also, 2 items from the mood module (fatigue and sleep) are scored 0 (“not at all”), 1 (“several days”) or 2 (“more than half the days” or “nearly every day”). Scores of 5, 10, and 15 represent thresholds for low, medium, and high somatic symptom severity, respectively.

GAD-7 Anxiety Severity Score. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of “not at all,” “several days,” “more than half the days,” and “nearly every day,” respectively. GAD-7 total score for the seven items ranges from 0 to 21. Scores of 5, 10, and 15 represent thresholds for mild, moderate, and severe anxiety, respectively. Though designed primarily as a screening and severity measure for generalized anxiety disorder, the GAD-7 also has moderately good operating characteristics for three other common anxiety disorders – panic disorder, social anxiety disorder, and post-traumatic stress disorder. When screening for anxiety disorders, a recommended threshold for further evaluation is a score of 10 or greater.

Rivermead Post-Concussion Symptoms Questionnaire (see above)

Modified Perceived Quality of Life Scale
MPQOL is a measure of the degree of personal satisfaction with one's level of functioning across several activities of daily living. Higher scores in the MPQOL scale reflect higher perceived satisfaction with current level of functioning. Thus, this scale measures "positive" affective-related ratings about functioning while the FSE measures "negative" affective-related functional limitations.

'Percent-Back-to-Normal' rating scale (PBNRS)
PBNRS is a global measure of patient self-reported recovery or the degree to which the patient perceives she or he falls between no post-TBI or PTSD recovery (i.e., 0% = not at all back to normal) and complete post-TBI or PTSD recovery (i.e., 100% = complete recovery or back to normal).

'Return to school or work'
This will be assessed by simple questioning. Subjects will be asked if they have returned to work/duty and, if so, if they returned to the previous employment or a different job, and if the new job is commensurate with the old job. Return to pre-morbid level of functioning will be assessed with the PBN.

Neurological Examination
The neurological exam will be performed by the P.I. The patients will be questioned for previous neurological disease. Neurological exam will emphasize balance and gait, two functions that have been found to be abnormal on physical exam in patients with mild or moderate chronic TBI.

Imaging
Imaging is not required for participation; it is optional and may be obtained anywhere. Imaging data obtained elsewhere will be collected and reviewed upon enrollment. However, if imaging is received from patients, the results will stored in the database for potential future study.

HYPERBARIC OXYGEN THERAPY (HBOT) PROCESS

Subjects will be treated in various types and sizes of hyperbaric chambers. Patients may undergo treatment in either a multiplace or monoplace chamber. The above description is for the 100% monoplace oxygen chamber which will be the most common chamber used in this study since it is the most common chamber in freestanding and hospital-based centers.

Patients will be instructed before treatment on how to equalize the pressure in their middle ears. Once inside the chamber, just after closure of the chamber door and immediately before pressurization, the subject will be instructed to perform the first Valsalva maneuver to pressurize the middle ear space before the initial 1.5 pounds per square inch (psi) start-up pressurization of the chamber that attains air-tight "seal" of the chamber. This maneuver

expands the middle ear space and brings the ear space to neutral volume after the compression effect of the initial 1.5 psi seal pressurization.

Pressurization will proceed with 100% oxygen at 1.0 pounds per square inch (psi) per minute, the lowest pressurization rate, to 1.5 ATA (atmospheres absolute) or 7.35 psi and will take approximately 7 minutes. During the entire pressurization the subject will be continuously instructed to "clear his/her ears" using various pressure equalization techniques that they have learned and practiced before chamber entry. Inability to pressure-equalize the middle ear space will immediately truncate pressurization until the subject can equalize pressure. Pressurization will then resume until the final depth of 1.5 ATA is achieved. The subject will be notified when he/she is at treatment depth. The subject will remain at depth for approximately 45 minutes and the subject will be informed of the onset of depressurization which will occur at the same rate as pressurization. The subject will again be instructed to pressure equalize the middle ear space, however, barotrauma is minimized during decompression since gas expansion in the middle ear space passively vents through the Eustachian Tube to the pharynx. Total hatch-to-hatch dive time will be 60 minutes. The subject will be queried regarding pain and untoward symptoms after this and all subsequent treatments.

Multiplace Chambers

Alternatively, depending on the facility that provides the HBOT subjects will be treated in a chamber that can accommodate multiple patients. In this chamber the subject will breathe air as the chamber is compressed. Once the chamber pressure reaches one and one half times atmospheric pressure the subject will have a clear plastic hood placed over their head that will be secured with a rubber neck dam to prevent oxygen leak. The subject will breathe 100% oxygen in this hood for 50 minutes. The hood will then be removed and the chamber brought back to surface pressure while the subject breathes chamber air. The hatch-to-hatch dive time will be 60 minutes.

DATA ANALYSIS AND MONITORING

Administrative Coordination of All Sites

We anticipate multiple sites will participate. A main Administrative Project Coordinator (APC) will be hired to ensure consistency and accuracy among all sites [each site will have its own study coordinator]:

- Assurances: all sites will obtain a Federal Wide Assurance as well as a Department of Defense Assurance/Addendum (if applicable)
- Training: all investigators and key personnel will complete required human subjects and GCP training (CITI) and appropriate protocol-specific training.
- Oversight and Monitoring: the APC will ensure that all required monitoring of the research is scheduled, completed, and documented at the required time schedules.

Site Monitor

The site monitor will perform site/clinical monitoring to assure high quality trial conduct. As

such, they will perform:

- On-site monitoring of individual case histories; assess adherence to the protocol; i.e., ensuring that all subjects have gone through the appropriate consenting process and have signed the most current consent documents.
- Ensure the ongoing implementation of appropriate data entry and quality control procedures;
- Conduct a general assessment of GCPs

Data Collection, Storage & Confidentiality

Data collection and management of the NBIRR master database will be performed using the CareVector Platform™ (CVP). The CVP is accessible via the Web from a site computer. Research data collected by each site will be stored locally on a site hard drive as primary data. Only persons authorized by the site PI will have access to the data on-site, and each site PI will be fully briefed on the rules of confidentiality. Concurrently, data from all sites will also be stored on the CVP, with all patient names encrypted. The only subject identifiers what will be available on-site will be encrypted file names, and these only for audit and analytical purposes.

The platform also allows for the oversight of the process and sites. It has a built in Auditor role that will support data and safety monitoring functions. Security procedures are a built-in aspect of the CVP, with multi-role and multi-site access-controls. Password protection and access privileges are granted by security administrators, each of whom has Department of Defense security clearances and who have built similar systems for DoD and the commercial sectors.

A CareVector server will house the composite database, with a backup copy stored at a remote location. All data are secured, stored and backed up according to state-of-the-art security protocols at both locations.

The platform with the database ensure that all data entered will be available for daily viewing by the co-PIs for analysis, audits, quality control, and for study throughout the trial. Security is provided via 128-bit SSL encryption across all public channels; database encryption of sensitive items such as patient names and passwords; multiple border and edge firewalls; and F5 load balancing, providing redundancy and 99.9% uptime guarantee. Training and support for the CVP are provided as a part of the orientation process for the study and are a prerequisite for site participation.

DATA SAFETY & MONITORING BOARD (DSMB) & PLAN

DSMB Responsibilities

The DSMB will be responsible for examining safety and efficacy data and other records for protocols on an explicitly defined schedule. The DSMB will communicate results and minutes from meetings to the administrative coordinator in a timely fashion.

Termination of the study would only occur for safety reasons should an inordinate number of adverse events appear in the study subjects. Given the long and safe track record of HBOT 1.5, this is not anticipated.

DSMB composition

A DSMB will be created and comprised of the following individuals who will be free of apparent financial and non-financial conflict of interest:

- Clinician or neurophysiologist with prior relevant experience in the use of hyperbaric chamber therapy, neurological disorders, etc
- biostatistician
- ethicist

DSMB Frequency of meetings

These will be monthly or ad hoc as needed.

- An initial meeting will occur before the start of the research
- Subsequent meetings will occur on an agreed scheduled as determined during the initial DSMB meeting.

Sample Size

As a large scale, multicenter, observational study of the positive effect of a safe treatment, the objective is to study with sensitive measures, large numbers of subjects so as to not be limited by sample size. Nevertheless, a discussion of sample size for a small study is described below.

A sample size analysis and projection for a small pilot study was prepared based on an intent to generate trends of data only. Previous estimates of sample size for a randomized prospective study of HBOT in chronic TBI/PCS were based on a series of 4 chronic TBI patients, three of whom had mild TBI and one severe TBI, who completed a variety of psychometric tests before and after HBOT treatments.

The Wechsler Memory Scale-Delayed Memory standard scores was a psychometric test that all four patients had completed and was used to provide an approximate sample size projection. Since a true control group was lacking in this series of patient data, we assumed that a control group would demonstrate minimal practice effects. The effect size observed was assumed to continue and was of sufficient clinical interest to be used as the basis for the estimation of the minimum sample size. Sample sizes of at least 25 in each group would insure that the effect size of interest (or larger) could be detected using two-group

ANOVA model with at least 80% probability (power). These projections were based on a very small sample size, assumptions of little or no change in a hypothetical untreated group, and the fact that the overall change in memory was significantly influenced by the performance of a single patient who experienced a dramatic improvement in memory after HBOT. As a result, the power analysis could only be considered a crude estimate of the sample sizes necessary to detect a significant improvement in the single cognitive function of memory for a randomized trial. To establish trends, however, it is estimated that 60% of the above 25 subject groups, or 15 subjects with TBI and 15 subjects with TBI/PTSD, would be sufficient. This number would also take into account 10-20% of the subjects who maybe found to be malingering and have been misdiagnosed by outside diagnosticians.

An N=1,000 was chosen so that the actual population of brain injured civilians or veterans injured during the war could be examined. Cohorts who have similarities (such as those who have had cardiac arrest or CO poisoning before or after their TBI) can be tracked and analyzed as a group.

Statistical Methods

Because of the anatomic heterogeneity of traumatic brain injury, there is heterogeneity of symptoms, cognitive deficits, and emotional/psychological effects. Some patients may have greater or lesser deficits in different cognitive functions for near identical injuries. Assuming these deficit functions are due to injuries to specific areas of the brain and hyperbaric oxygen would simultaneously treat all areas of injured brain, greater or lesser improvements will occur in these functional domains. The primary aim of the study is to determine whether treatment with HBOT significantly improves cognitive functioning in TBI as well as TBI/PTSD.

Since there are several variables that assess cognitive functioning, we will employ the sum testing method of O'Brien[167]. This method calls for the conversion of all psychometric test scores in the complete battery on a given individual to z-scores and sums of these z-scores and obtains a single composite value for each individual to represent cognitive functioning.

Transition from Research Participation

Upon completing treatment, patients will be provided instructions about what to expect and how to follow up with their physicians and other care providers. Participants in the study will be monitored longitudinally to ascertain the long-term outcome of their condition and how they may have been affected by the treatment rendered during the study. There may be a subset who require additional HBOT 1.5 treatments. (Some severely injured persons have had nearly 200 treatments.) If additional treatments are provided, those additional treatments will be tracked longitudinally and appropriate automated testing will be obtained whenever possible.

[167] O'Brien PC. Procedures for Comparing Samples with Multiple Endpoints. Biometrics, 1984;40:1079-1087.

RISK – BENEFIT ASSESSMENT

This is a no significant risk study using an existing FDA-cleared HBOT device.
At a recent DoD-DCoE consensus conference on HBOT in TBI, it was the group's consensus that HBOT at 1.5 ATA 100% O2 was completely safe.[168] At 1.5 ATA, there is no known risk other than claustrophobia or a perforated eardrum in the event of emergent rapid decompression. At 2.0 ATA, HBOT is still considered safe, with a seizure incidence of up to 3%. However, this pressure will not be used; at 1.5 ATA, the induced seizure risk is considered to be zero.

General safety considerations and protection against risks
Significant adverse events will be defined as those requiring emergency department evaluation or hospitalization. Pulmonary barotrauma manifest by pneumothorax or air embolism, inner ear barotraumas with round or oval window rupture, and oxygen toxicity manifest by grand mal seizure would be the most serious adverse events, but are unanticipated. An oxygen toxicity seizure is a rare occurrence at high pressures. The low pressure featured in this study has not been reported to cause seizures and has been used to treat childhood seizures in China and in the United States. In Dr. Harch's clinical experience these severe adverse events are exceedingly rare in this study's subject population and have only been seen a few times in the past 22 years.[169]

The most likely anticipated adverse events would be middle ear and sinus barotraumas. They are most common in the young and elderly, neither of which will be subjects in this study. Transient emotional liability is expected in less than 10% of the study group, but is managed with informed consent and bedside counseling. An additional possible adverse event would be a global deterioration in symptomatology due to incorrect dosing. This has only been seen in patients with TBI who have also suffered a global ischemic event such as cardiac arrest, severe prolonged hypotension, or severe prolonged hypoxia. In the PI's experience this deterioration can be ascertained early and appropriate changes in dosage made without terminating treatment.

Nevertheless, the site PI under oversight of the DSMB will review each subject's progress, looking for these and any other anticipated or unanticipated adverse event, report significant adverse events to the IRB, and monitor the overall study for adverse trends. Individual adverse events will be managed on a case-by-case basis and a decision made by the PI and the DSMB as to whether the subject should continue in the study. Should 30% (three) of the first ten subjects experience significant adverse events as defined above, the study would be stopped, pending full review of all of the events.

Secondary gain for malingering and disability
This is always a problem in mild-moderate TBI research, however the degree of malingering is always difficult to assess absolutely. To prevent elimination of patients with

[168] DoD "HBOT for TBI" Consensus Conference White Paper, 28 October 2008.
[169] Sheffield, P.J.; Sheffield, J.C.; "Complication Rates for Hyperbaric Oxygen Therapy Patients and their Attendants: A 22-year Analysis," Proceedings of the Fourteenth International Congress on Hyperbaric Medicine, San Francisco, California, USA, Editors: Fredrick S. Cramer, Paul J. Sheffield. pp. 312-318.

bona fide brain injury who have may have assumed a sick role and have some degree of embellishment we will include all patients regardless of level of effort/malingering. Some of these patients may have already been given disability. It is our objective to only determine whether we can improve patients who have been given military or civilian diagnoses of chronic TBI/PCS and/or TBI/PCS/PTSD and which patients with these diagnoses will be susceptible to possible beneficial effects of HBOT. The inclusion of all patients regardless of effort can provide valuable information on the effectiveness or ineffectiveness of HBOT in all patients and identify/characterize those non-responders. The presence of disability payments will be noted so that this problem can be examined. It is anticipated that if patients can be treated BEFORE they receive a disability diagnosis, the level of disability will be reduced.

Concern About post-hoc revision of Military Disability Rating

For those who have already been disability rated by the military the subjects will be informed that their test results are private and cannot be accessed to personally identify them and re-rate their disability. This should help reduce bias in patient recruitment and ensure more valid testing. As some research subjects will be active duty, retired military, etc., complete confidentiality cannot be promised as access to these records can be obtained for subjects using military TriCare.

Training effect may improve performance on automated tests

We will employ measures that minimize learning effect. ANAM and CNSVS are designed to compensate for the learning effect using internal methods, such as the presentation of alternate examples. Further, we will have the subject take the test set twice before starting HBOT treatment.

Complications

Historically these have been minimal in adults with chronic TBI. Therefore, drop-out rate should be very small.

Drop-out rate

This should be minimized by the fact that this is a very short treatment protocol, at least for the first phase of 40 HBOT treatments.

Excessive amount of testing

The multiple tests are necessary due to the heterogeneity of TBI. Since there is no all-inclusive QOL measure, multiple questionnaires are necessary. To undergo the computerized test batteries the total test time is about two hours. This is substantially less than the amount of time for a full psychometric test battery.

Confinement Anxiety

Severely claustrophobic patients will be screened out by the physician before the Rivermead questionnaire is administered. Some of these patients may do fine with larger chambers as available. Xanax, as needed, will help those who still have problems, however, this will be discontinued one week before repeat testing.

Automated Cognitive Testing
Automated cognitive testing has limitations. However, when used to monitor change over time, it is valid.

Lack of sham control group
This is an observational study of an off-label use of an FDA-cleared device. This is acceptable because preliminary pilot data results showing efficacy suggest that a sham treatment arm may be unethical, especially since the data demonstrate that the treatment is extremely safe. And, because the first study by Dr. Harch was a pilot, it will be followed by a second single crossover study that is about to begin in parallel with the present study. Longitudinal measures can be analyzed for comparison to baseline. Also, performance of the subjects in this study can be compared to historical data accumulated by the military on the degree of spontaneous improvement over time in their untreated injured population of servicemen and women.

Alternative Methods & Approaches
While there are other therapies that are attempted for TBI and TBI/PTSD, we know of no safe, effective alternative treatment method for traumatic brain injury.

Alternative outcome measures are numerous and formal comprehensive neuropsychiatric testing may be superior to the automated approaches proposed herein. However, due to logistical, funding, and time constraints it is not possible to obtain the most comprehensive neuropsychological analyses or all possible imaging studies and biomarkers. Rather, we will make every effort to collect information on any testing or imaging ordered by the person's physicians in the routine course of their clinical care.

HBOT 1.5 Safety versus Drugs Prescribed Off-Label for PCS & PTSD
When comparing HBOT to the common drugs being prescribed off-label for PTSD and TBI patients, the difference is remarkable. (Only Zoloft is on-label for PTSD. No drugs are approved for PCS or TBI). Many of the anti-depressants have a warning label from the FDA. The actual FDA warning reads, "Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of (insert name of antidepressant) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24…" The age group described by this warning would seem to include a significant number of our brain-injured veterans. Thus, by getting this study done quickly, the investigators have a good chance of helping reduce the epidemic of suicides in the current population of casualties from the current war.

Potential benefits to the subjects
The subjects will not be given false assurance that they are likely to benefit from the procedure.

Patients will not be compensated and the study will be patient- or site-funded

The subjects will not be compensated for treatment. Actually, until higher levels of funding become available for this study, the subjects and or the site investigators will have to find private funding for their treatment as outlined in the present study.

Alternatives to participation

Congress has funded $1.9 billion in TBI & PTSD research since 2005. Therefore, the patient may choose to continue to participate in any one of the existing programs for patients with TBI and TBI with PTSD, using drugs and/or complementary therapies. It should be noted that there is no drug or device currently approved by the FDA to treat TBI or TBI with PTSD.

SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT / ASSENT

Method of Identification and Recruitment

Subjects will be recruited through multiple avenues, particularly through military channels or media reports. It is anticipated that a majority of the subjects will be current and former military suffering from TBI and PTSD. Our group anticipates media presentations to recruit subjects for this project. A number of military charities have funded individuals who have needed to travel to receive treatment.

In addition, each PI and the Sponsor Organizations have extensive relationships with professional societies which will be conduits to the target population. Print, radio advertisements/ announcements, and website announcements (the International Brain Research Foundation, the International Hyperbaric Medical Association, the American College for the Advancement of Medicine, the American Association of Health Freedom, the American Association of Physicians and Surgeons and others) will also be used to recruit subjects. Additionally, TBI associations and support groups nationally will be targeted for presentations and announcements.

Lastly, due to the nearly 200 direct presentations to congressmen/women, senators, their staffs, military conferences, Wounded Warrior meetings, treatment of current and recently disabled injured military, the PI's and the Consortium have deep and extensive connections with the U.S. Congress, multiple veterans organizations, and their support groups. All of these individuals and organizations will be contacted to announce this study. The study will be further supported by a very popular website of Dr. Harch which will have a special section devoted to this study.

Process of consent

Each subject will be provided the consent form and will be provided at least 24 hours to review, consider, ask questions, and sign the consent form. The subject will be provided a copy of any document they sign and two copies will be made for storage on site and at the central office of the sponsor.

Subject capacity

All subjects will have the capacity to consent to treatment. The rare subject will not be able to read due to an eye injury or brain injury. These subjects will have the consent form read to them twice in the presence of a witness and then, the reader and witness will sign the patient's consent form in lieu of the patient.

Subject/representative comprehension

Referring organizations or volunteer veterans service organizations will receive a briefing on the study, risks, benefits, etc., and for those who are calling veterans, a script and training through CITI will be provided before soliciting subjects for the study. It is further anticipated that the website will reflect current data regarding patients treated to date and anonymous outcomes data.

Debriefing procedures

All subjects will be briefed by the investigator or designated personnel in accordance with best medical practices for full disclosure of patient outcomes, anticipated future status, and how to return for more treatment, if desired.

Costs to the subject

The subject is responsible for all costs. You will not be paid for your participation or reimbursed for your time and travel.

Multiple efforts are underway to provide funding from outside sources. At this time, the sponsor does not have the funds to pay for the treatment.

The sponsor will pay for all of the automated neuropsychiatric testing, coordination of the study, and collection of data. If the sponsor or funding source does not pay for the treatments and procedures the patient will be responsible for the costs of the study. It is anticipated that the insurance company will not cover the costs of the treatments in this protocol, because the protocol is considered experimental.

Medicare, in particular, makes it very clear that they do not cover costs that are incurred as part of a research protocol. This protocol is an observational protocol and the use of HBOT therapy for this condition is considered investigational – this is why the present study is being done.

Ancillary diagnostic testing that is NOT required by the study may be recommended by the subjcet's physician/s. For purposes of planning and estimation, the subject will be informed of the costs of testing that are NOT required in this study are: psychometric screening, evaluation, and quality of life questionnaires ($1000/exam; subjects who undergo testing by a neuropsychologist will have 2 or 3 of these), MRI of the brain with radiologist's reading ($2,000), SPECT brain imaging with radiologist's reading ($1,750 per SPECT; subjects will have 3 or 4 of these), and functional brain MRI (approximately $2,000 per study; there could be 2-3 of these tests).

The principal investigator will arrange for medical care for any emergency medical problem that the subject may experience as a direct result of their participation in this research. This will be provided on a fee-for-service basis. There are no funds available to pay for any disability, study related, or unforeseen complications that result from participation in this study or for damages such as lost wages, etc.

The costs of testing and treatment that are required for this study are: hyperbaric medicine evaluation, screening, and exam ($450), HBOT (approximately $200/HBOT-this will vary according to the center at which the subject receives his HBOT; subjects will have 40-80 of these), pregnancy tests during the course of the study ($30 each; female subjects will have 3 or 4 of these); transportation costs to and from the city with the hyperbaric clinic or hospital (will vary according to the subject's proximity to the center), and lodging/food/transportation costs to and from testing and treatment centers ($100-150/day; subjects will be in the treatment phase of the study for 6-19 weeks. Follow-up computer testing will occur at 6 and 12 months).

There are some tests that may be recommended by the patient's physician, however, these are not part of the study unless expressly stated elsewhere in this consent form. Costs of additional testing, such as EEG, angiograms, MRI, CT, or PET imaging, or Doppler studies should be discussed by the patient with the ordering physician. These tests can vary in cost and may or may not be covered by insurance. These tests are not required for the study.

Payment for participation

Other than expense reimbursements from charities or VA travel or Temporary Duty pay that several active duty military have received, the only payback – as opposed to payment -- to the patient is expected to be a significantly improved life from the acute relief of PCS symptoms and restoration of neural function. There has not been a great deal of need to provide incentive payments for participation. These families and individuals, however, are generally financially incapacitated by their disability and therefore third party payment is needed.

APPENDICES

APPENDIX I.
Complication Rates for Hyperbaric Oxygen Therapy Patients and Their Attendants: A 22-year Analysis

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APPENDIX I. Complication Rates for Hyperbaric Oxygen Therapy Patients...: a 22-year analysis

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COMPLICATION RATES FOR HYPERBARIC OXYGEN THERAPY PATIENTS AND THEIR ATTENDANTS: A 22-YEAR ANALYSIS

P.J. Sheffield, J.C. Sheffield

International ATMO, Inc, Nix Wound Care and Hyperbaric Medicine Center, Nix Medical Center, San Antonio, Texas

INTRODUCTION

During the 22-year period from November 1979 through December 2001, approximately 8,200 patients received 170,000 hyperbaric oxygen (HBO) treatments at civilian multiplace hyperbaric facilities in San Antonio, Texas (1). Patients breathed oxygen via hood assembly while pressurized inside large walk-in chambers. Complications sometimes required removal from oxygen or removal from the chamber. This is an update of previous reports on patient and inside attendant complication rates (2,3).

MATERIALS AND METHODS

Patients were fully evaluated by the attending hyperbaric medicine physician prior to each treatment exposure. Fully trained hyperbaric physicians, nurses, and technical personnel provided constant attendance. A qualified medical attendant accompanied patients inside the chambers. The attendant supervised the treatment and managed complications under the direct supervision of an attending physician. Patients who could not be medically managed while receiving oxygen were either removed from oxygen or removed from the chamber. The incident was recorded on the hyperbaric chamber treatment log, and a list of complications was reported in annual Quality Improvement Activity Reports. The data for this paper were obtained from the hyperbaric chamber treatment logs and from Quality Improvement Activity Reports.

RESULTS

Table 1 contains the patient and inside attendant exposures on the various treatment protocols. Hyperbaric treatments were conducted at maximum pressures of 6 ata (6.06 MPa) for 11 gas embolism patients, 3 ata (3.03 MPA) for 178 carbon monoxide poisoning and 44 gas gangrene patients, and 2.82 ata (2.83 MPa) for 53 decompression sickness patients. For the remaining 7,943 patients with other disorders, the maximum treatment pressure was 2.36 ata (2.38 MPa). During this period, there were 170,096 patient treatment exposures and 82,400 inside attendant exposures.

Table 1. Treatment Protocols: Patient and Attendant Exposures (Attendant Breathes Air Throughout, Except at Decompression Stops)

Treatment Table	Max Pressure	Total Exposure (hrs:min)	No. Patient Treatments	No. Attendant Exposures
CO Poisoning	3 ata (66 fsw)	2:06	184	360
Decompression Sickness TT5: 45 min at 2.8 ata TT6: 75 min at 2.8 ata TT6: 100 min at 2.8 ata	2.8 ata (60 fsw)	2.15 4:45 6:25	139	410
Gas Embolism TT6A: 30 min at 6 ata	6 ata (165 fsw)	+7:30	25	50
Gas Gangrene	3 ata (66 fsw)	2:02	534	1,060
Wound Healing	2.36 ata (45 fsw)	2:10	169,214	80,520
Total Exposures			170,096	82,400

Table 2 contains the complication rates for 8,229 patients undergoing 170,096 HBO treatments. There were 1,417 complications that resulted in removal from the chamber, for an incidence of 83 per 10,000 exposures. The 10 top reasons for removal from chamber were: ear barotrauma (45/10,000 exposures), sinus barotrauma (8/10,000 exposures), claustrophobia/anxiety (7/10,000 exposures), abdominal pain/diarrhea (5/10,000 exposures), nausea/vomiting (5/10,000 exposures), chest pain (3/10,000 exposures), unable to autoinflate ears despite PE tubes (2/10,000 exposures), refusal to continue treatment (2/10,000 exposures), seizure (2/10,000 exposures), and doctors/ other appointments (1/10,000 exposures).

At Table 2 there is a list of 473 complications that resulted in temporary removal from oxygen while undergoing treatment in the chamber, for an overall incidence of 28 per 10,000 exposures. The ten top reasons for removal from oxygen were: nausea/vomiting (9/10,000 exposures), claustrophobia/ anxiety (6/10,000 exposures), hypoglycemic reaction (5/10,000 exposures), congestion/shortness of breath/trouble breathing (1/10,000 exposures), chest pain (1/10,000 exposures), agitation/combative (1/10,000 exposures),

Table 2. HBO Complication Rates at San Antonio Civilian Multiplace Hyperbaric Facilities During 1979 thru 2001				
	Removed from Chamber		Removed from Oxygen	
Years 1970-2001				
No. of Patients: 8,229		Occurrences		Occurrences
No. Exposures: 170, 096	Total	per 10,000	Total	per 10,000
COMPLICATION	Occurrences	Exposures	Occurrences	Exposures
Agitation, Combative	4	0.2	14	0.8
Barotrauma - Ear	759	44.6	0	0.0
Barotrauma - Sinus	130	7.7	0	0.0
Barotrauma - Teeth	5	0.3	0	0.0
Claustrophobia/Anxiety	117	7	102	6.0
Clear Tracheal Secretions	0	0	2	0.1
Congestion/SOB/Diff Breathing	32	1.9	24	1.4
Contaminants in Chambers - Fumes	0	0	6	0.4
Coughing	0	0	10	0.6
Disorientation/Hallucinations	7	0.4	0	0.0
Dizziness/Weakness	1	0.1	7	0.4
Doctors/ Other Appointments	25	1.5	0	0.0
Eyes Irritated	0	0	2	0.1
Equip Failure - Pacemaker, IV	3	0.2	8	0.5
High Blood Pressure	0	0	1	0.1
Hot Flashes/Overheated	0	0	12	0.7
Hyperventilation	7	0.4	3	0.2
Hypoglycemia	9	0.5	82	4.8
Nausea/Vomiting	77	4.5	149	8.8
Nosebleed	0	0	2	0.1
Oxygen Toxicity/Tingling	0	0	4	0.2
Pain - Abdomen/Diarrhea	88	5.3	3	0.2
Pain - Chest	44	2.6	16	0.9
Pain - Headache	2	0.1	0	0.0
Pain - Other	6	0.4	2	0.1
PE Tubes - Unable to Autoinflate	37	2.2	0	0.0
Pulmonary Edema	1	0.1	0	0.0
Refused to Continue Treatment	30	1.8	9	0.5
Seizure	29	1.7	7	0.4
Shakiness, Tremor	1	0.1	8	0.5
Social/Family Problems	2	0.1	0	0.0
Unresponsive	1	0.1	0	0.0
Total/Incidence Per 10,000 Exposures	1,417	83.4	473	27.8

hot flashes/overheated (1/10,000 exposures), coughing (1/10,000 exposures), refusal to continue treatment (1/10,000 exposures), and shakiness/tremor (1/10,000 exposures).

DISCUSSION

Patient Treatments

HBO therapy was provided for disorders on the accepted indications list of the Undersea and Hyperbaric Medical Society (4). Current accepted indications are:

1. Air or Gas Embolism
2. CO Poisoning, Co Poisoning Complicated by Cyanide Poisoning
3. Clostridial Myositis and Myonecrosis (Gas Gangrene)
4. Crush Injury, Compartment Syndrome, and Other Acute Traumatic Ischemias
5. Decompression Sickness
6. Enhancement of Healing in Selected Problem Wounds
7. Exceptional Blood Loss Anemia
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections
10. Osteomyelitis (Refractory)
11. Radiation Tissue Damage (Soft Tissue and Bony Necrosis)
12. Skin Grafts and Flaps (Compromised)
13. Thermal Burns

Patient Treatment Profiles

While pressurized inside the chamber, patients breathed oxygen with intermittent air breaks. Inside medical attendants breathed air throughout the course of treatment but breathed oxygen during decompression stops. Following are the typical treatment profiles to which the patients were exposed.

1. Carbon Monoxide Poisoning: Pressurize in 5 min to 3 ata, remain for 51 min, ascend to 2 ata in 5 min, remain for 55 min, and depressurize to surface in 10 min. This table could also be extended so that the patient might remain at 2 ata for up to 175 min.
2. Decompression Sickness: Pressurize to 2.82 ata and decompress on USN TT5 or USN TT6 (5).
3. Air or Gas Embolism: Pressurize to 6 ata and decompress on USN TT6A (5). After 1998, treatments included pressurization to 2.82 ata and evaluating the patient for continuation of treatment at 2.82 ata or at 6 ata with subsequent decompression on USN TT6 or TT6A.

4. Gas Gangrene: Pressurize in 5 min to 3 ata, remain for 107 min, depressurize to surface. Attendants who remained inside the chamber for the entire duration of the treatment breathed 100% O_2 for 37 min at 1.9 ata plus the 2 min depressurization to surface.
5. Wound Healing: Pressurize in 5 min to 2.36 ata, remain for 110 min, then decompress to surface in 10 to 15 min, depending on condition of patients.

Patient Complications

Ear barotrauma (45/10,000 exposures) and sinus barotrauma (8/10,000 exposures) were the primary reasons for removal from the chamber, whereas nausea/vomiting (9/10,000 exposures) and claustrophobia/anxiety (6/10,000 exposures) were the primary reasons for removal from oxygen. This is consistent with previous reports from this institution (2,3) and from other centers (6,7). Of the 8,229 patients, 1,413 (17%) did not complete a full course of HBO (1). In some cases severe complications resulted in termination of the HBO treatments by the attending hyperbaricists. Some did not complete the treatment course because of failing health. Some were discontinued for logistical reasons or by order of their attending physicians. Others stopped for personal reasons, with the usual reason being claustrophobia or confinement anxiety. There were 117 events (8.3% of complications) of confinement anxiety that resulted in removal from the chamber. An additional 30 (0.36%) started the treatment and refused to continue. There were occasional potentially life-threatening events (congestive heart failure, suspected heart attack, seizure, pacemaker failure, pulmonary edema, and excessive tracheal secretions) that resulted in removal from the chamber, but none resulted in fatality at the hyperbaric facility.

Attendant Decompression and Complications

Usually, unhealthy staff members were not scheduled as inside attendants, but an average of 3 - 4 events occurred annually in which ear, sinus, or tooth barotrauma resulted in inside attendant removal from the chamber.

For safe decompression to surface, inside medical attendants used U.S. Air Force modifications to the U.S. Navy Standard Air Decompression Tables (8), which reduced the maximum U.S. Navy allowed total bottom time by five minutes. Maximum exposures are at Table 1. During the entire 22 years of operation, inside medical attendants were exchanged mid-treatment in an attempt to keep their decompression obligation within "no decompression limits." For example, two air-breathing inside attendants divided the 110-min time during each of the 40,250 elective wound-healing treatments profiles at 2.36 ata (80,500 attendant exposures). Treatment of other disorders accounted for 1,900 inside medical attendant exposures. Thus, there were

82,400 inside medical attendant exposures shared by 200 individuals during the 22 years of operation.

Decompression sickness in inside medical attendants is rare and has been previously documented (9). Five attendants presented with questionable symptoms after exposure to 2.36 ata and were subsequently treated for DCS, an incidence of 0.006% (5 cases in 80,500 exposures). DCS episodes also occurred in two inside medical attendants on a single, 6-ata gas embolism treatment. Both attendants performed hard labor at 6 ata as a previously comatose patient improved and went through a combative period. Despite oxygen decompression, both attendants required HBO for limb pain within six hours after the exposure (2). The HBO treatment has not produced any cases of DCS among patients in over 170,000 exposures.

CONCLUSIONS

In this large patient series, the incidence of complications requiring removal from oxygen or removal from the chamber was very low (approximately one percent of exposures). The occasional potentially life-threatening events were appropriately managed without fatality by fully trained, competent staff.

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APPENDIX II. Case report: Treatment of Mild TBI with Hyperbaric Oxygen

Colonel James K. Wright, USAF, MC, SFS*
Eddie Zant, MD**
Kevin Groom, PhD***
Robert E. Schlegel, PhD, PE****
Kirby Gilliland, PhD****

*720th Special Tactics Group
223 Cody Avenue
Hurlburt Field, FL 32544

**Hyperbaric Medicine Inc.
913 MarWalt Drive
Fort Walton Beach, FL 32547

***The Anchor Clinic, LLC
996 Airport Road
Destin, FL 32541
****Center for the Study of Human Operator Performance
The University of Oklahoma
3200 Marshall Avenue, Suite 260
Norman, OK 73072

Abstract: Two United States Air Force Airmen were injured in a roadside improvised explosive device (IED) blast in Iraq on 13 January 2008. Both airmen suffered concussive injuries and developed irritability, sleep disturbances, headaches, memory difficulties, and cognitive difficulties as symptoms of mild traumatic brain injury (mTBI). Six months after injury, repeat Automated Neuropsychological Assessment Metrics (ANAM) testing showed deterioration, when compared to pre-injury baseline ANAM assessment, in all measured areas (simple reaction time, procedural reaction time, code substitution learning, code substitution delayed, mathematical processing, and matching to sample). The airmen were treated with hyperbaric oxygen (HBO) in treatments of 100% oxygen for one hour at 1.5 atmospheres absolute resulting in rapid improvement of headaches and sleep disturbances, improvement in all symptoms and resolution of most symptoms. Repeat ANAM testing after completion of the hyperbaric treatments, nine months after initial injury, showed improvement in all areas, with most measures improving to pre-injury baseline levels. The airmen received no other treatment besides medical monitoring. Repeat neuropsychologic testing confirmed the improvement. We conclude that the improvement in symptoms and ANAM performance is directly attributable to the HBO treatment.

Introduction:

Traumatic Brain Injury has been called one of the signature injuries of Operations Enduring

Freedom and Iraqi Freedom. The Rand Report documented a 19% self-reported incidence of probable TBI among returning service members with 320,000 probable TBI cases, most of which (80%) are mTBI[170]. Per case one year costs for mTBI were estimated at $27,259 to $32,759 in 2007[171]. The lifetime costs of even mTBI impairment in young service members would seem to be almost incalculable[172].

Mild TBI is characterized by a concussive event causing a brief period of unconsciousness (less than thirty minutes) or a period of confusion or amnesia lasting less than 24 hours. The Glasgow Coma Scale is 13 to 15 and imaging studies are also usually normal. Since the symptoms of mTBI may develop gradually, are often subtle, and can be confused with other illness such as post traumatic stress disorder, mTBI may be unrecognized and undiagnosed[173]. A concussive injury causes diffuse axonal injury, structural neuronal damage, and diffuse neuronal dysfunction[174]. The symptoms of mTBI are variable and may include headache, irritability, impulsivity, anger, cognitive impairment, memory difficulty, loss of executive function, vestibular and sleep disturbances[175]. Electroencephalogram and sleep studies are usually normal. Most individuals with mTBI recover in 3 to 12 months, especially those who are young[176]. However, some victims do not recover, or only recover slowly, and are at risk for future injury and deterioration of brain function[177]. Treatment of mTBI has included rest and observation, education, cognitive rehabilitation, and pharmacotherapy[178]. Pharmacologic treatment may be required for control of disabling symptoms of headache, irritability, depression, and anger[179].

Case Report:

On 13 January 2008 Airman B, a 23-year-old male vehicle operator, was a convoy Lead Vehicle Commander (LVC) sitting in the passenger seat of an M915 14-ton truck and Airman C, a 22-year-old male vehicle operator, was driving the vehicle that was attacked with an improvised explosive device (IED). The detonation occurred on the passenger side of the vehicle, nearest to where Airman B was sitting. (Figure 1) The vehicle was damaged and Airmen B and C sustained concussive injuries with a sense of being dazed for several minutes. There was no known direct blow to the head for either occupant or loss of consciousness, although both occupants had tinnitus and Airman B, who was approximately three feet closer to the blast, suffered immediately from a severe headache. Airman C continued to drive the damaged vehicle for several minutes. Airman C had no

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immediate symptoms other than being slightly dazed, but developed a mild headache some hours later. Later in the day, Airmen B and C reported to the medical clinic where no additional injuries were found; they were given acetaminophen for their headaches and placed on light duty. Airman C found relief from his headaches with acetaminophen and Airman B's headaches persisted for several days along with lightheadedness and fatigue. Two weeks later their symptoms had largely resolved and they were returned to full duty.

Three weeks post-injury both airmen noted the return of headaches with difficulty sleeping. Airman B expressed his headache severity as 5-6 and Airman C as 4-5 (on a scale of 10 with 10 being the most severe pain imaginable) with headaches occurring daily and lasting for several hours. Both individuals had difficulty falling asleep and remaining asleep, and they reported sleep duration of 3-6 hours per night. Additionally both individuals felt they were quick to anger and stayed angry from trivial provocations for several hours. Lack of attention to detail, forgetfulness, and fatigue were also reported by both airmen. These latter symptoms began insidiously about three weeks after injury, progressed for about two months and remained constant for the next four months until treatment with HBO was administered.

Upon arrival at their home base the airmen presented to the Battlefield Airman Clinic complaining of headaches, fatigue, lapses in memory, irritability, and sleep disturbances. Neurological exams were normal although the airmen appeared tired. Computerized tomography of the brain, EEGs, and sleep studies were normal. On initial deployment both airmen had received the Automated Neuropsychological Assessment Metrics test (ANAM) on 11 November 2007, two months prior to injury. This test was repeated on 21 July 2008, six months after injury. The repeat ANAM testing showed marked declines from the pre-injury baseline in several areas of measurement. **(Figures 2a and 2b)** Airman B presented a statistically significant change in Simple Reaction Time and Matching to Sample, along with declines in all other areas. Detailed neuropsychological testing of Airman B at six months post-injury, prior to HBO therapy, revealed a diffuse or scattered pattern of deficits. Although his IQ score was within the average range, his neuropsychological functioning on a summary measure (Repeatable Battery for the Assessment of Neuropsychological Status-RBANS Form A[180]) was at just the 7th percentile. Moreover, Airman B showed marked attention dysfunction for both auditory and visual material; cognitive processing speed was slowed and subjectively observed in casual conversation with the patient. He showed difficulty in repeating sentences and digit sequences as well as learning digit sequences over repeated trials. Airman B also demonstrated problems in both verbal learning and visual memory. His reading speed was slowed, fingertip-tapping speed was slowed in both hands, and clerical speed for coding tasks was mildly impaired. He showed difficulty for rhythm perception and visual-motor integration for copying geometric designs. His reaction time was slowed on a computerized measure of attention. Reading level for sight words remained at the college level, but written arithmetic was at just the 6th grade level.
Airman C presented statistically significant and drastic changes in both Simple Reaction Time modules (at the beginning and end of the battery), along with declines in all other

[180] Randolph, C. *Repeatable Battery for the Assessment of Neuropsychological Status*, San Antonio, TX: The Psychological Corporation, 1998.

areas except Mathematical Processing. Detailed neuropsychological testing of Airman C at the same time, prior to HBO therapy, was largely within normal limits notwithstanding problems for inconsistent attention and right upper extremity dysfunction for grip strength and somatomotor integration in the dominant right hand. His RBANS (Form A) total score was at the 50th percentile, average range.

Initially treatment of the headaches with ibuprofen and butalbital-aspirin-caffeine capsules (Fiorinal®) was tried, but these drugs were ineffective in relieving the pain. The airmen were placed on limited duty and daytime work only.

Because the two airmen had shown no improvement in their symptoms for seven months and were having difficulty performing their occupations, it was decided to begin hyperbaric oxygen (HBO) treatment. Treatment with HBO was begun eight months post initial injury. The treatment protocol was 100 % oxygen for one hour at 1.5 atmospheres absolute. Treatments were given 5 days per week. Clinical improvement was rapid. Airman C reported that his headaches vanished by the 5th treatment and did not return, and that he was able to sleep 7-8 hours per night uninterrupted. Airman B reported that his headaches weakened to 3-4 on a pain scale of 10, lasted only 1-2 hours instead of the previous 8 to 10 hours, and that he was able to sleep 8-9 hours per night uninterrupted. Both airmen reported that they felt more mentally alert and were less prone to forgetting, although they still did not feel “normal”. At the completion of the 40-treatment protocol, Airman C felt that his symptoms had ostensibly resolved and Airman B felt that he was much improved, notwithstanding some lingering irritability and forgetfulness.
Repeat ANAM testing showed improvement in essentially all areas for both airmen. Airman C’s ANAM scores returned to pre-injury baseline levels, and Airman B’s ANAM scores returned to pre-injury levels with no statistically significant differences in any of the tested domains. **(Figures 2a and 2b, and Figures 3a and 3b)** Repeat detailed neuropsychological testing of Airman B showed improvement on some but not all areas of cognitive functioning after HBO therapy at ten months post-injury. HisRBANS (Form B) total score was at the 12th percentile. For a patient with mild to moderate TBI, his scores improved faster than would be expected through spontaneous brain healing alone during this time interval. Areas of objective improvement included visuoconstructive abilities, fingertip tapping speed, and verbal learning/memory for word lists. His cognitive abilities status post HBO treatment were deemed satisfactory to continue his job duties without special monitoring.

Repeat neuropsychological testing of Airman C was generally consistent with his pre-treatment test scores. Areas of subtle improvement such as motor abilities in the dominant right hand, written arithmetic, and verbal fluency were observed. His RBANS-B total score was at the 47th percentile, which was not a significant change from pre-treatment testing.

Airman C was essentially well. Based on these results, it was decided to return Airman C to full duty, while Airman B continued hyperbaric treatment for another 40 treatments following the original treatment protocol. Repeat ANAM testing on Airman B at the conclusion of the second set of 40 HBO treatments showed improvement in all measures at or exceeding his pre-injury state, except for matching to sample, which was improved markedly from the injury state (Figure 2). Airman B reported that he had made continued improvement in cognitive function, felt much more alert, had returned to his pre-injury functional state; he was

sleeping uninterrupted eight hours per night, and that his headaches had diminished to about one per week of 2-3 in pain intensity and lasting 2-3 hours.

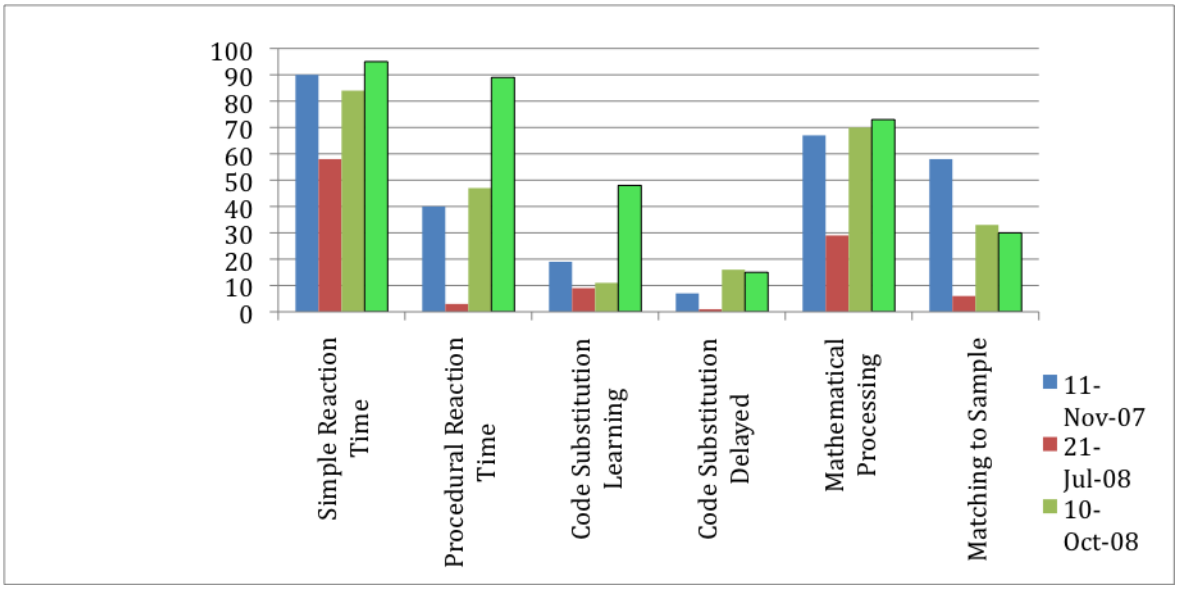

Figure 1a Airman B ANAM Scores. Scores are presented as the percentile of the comparison group of military members without TBI.

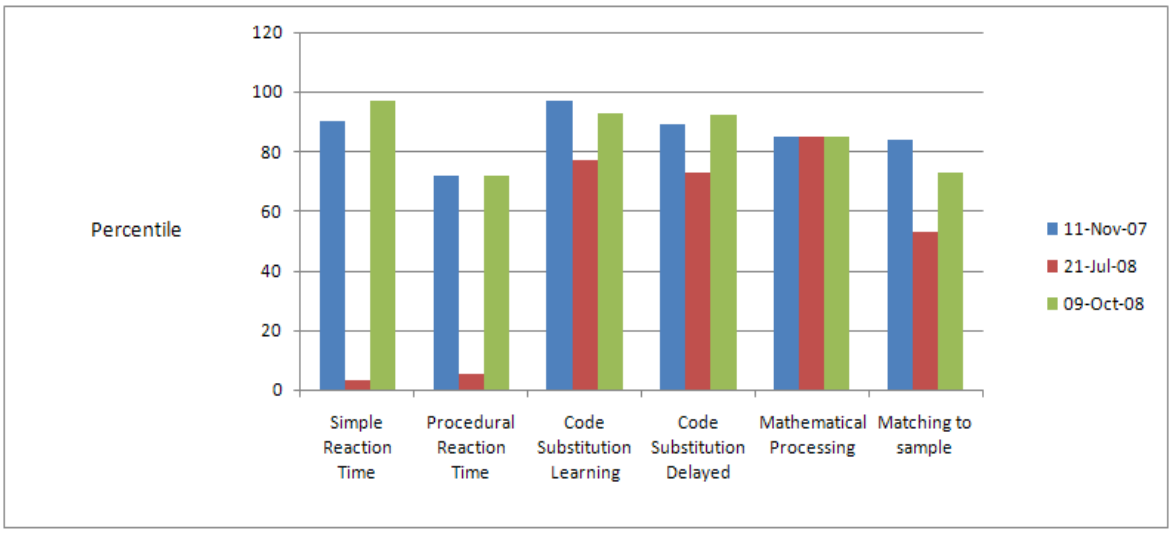

Figure 2b Airman C ANAM Scores. Scores are presented as the percentile of the comparison group of military members without TBI.

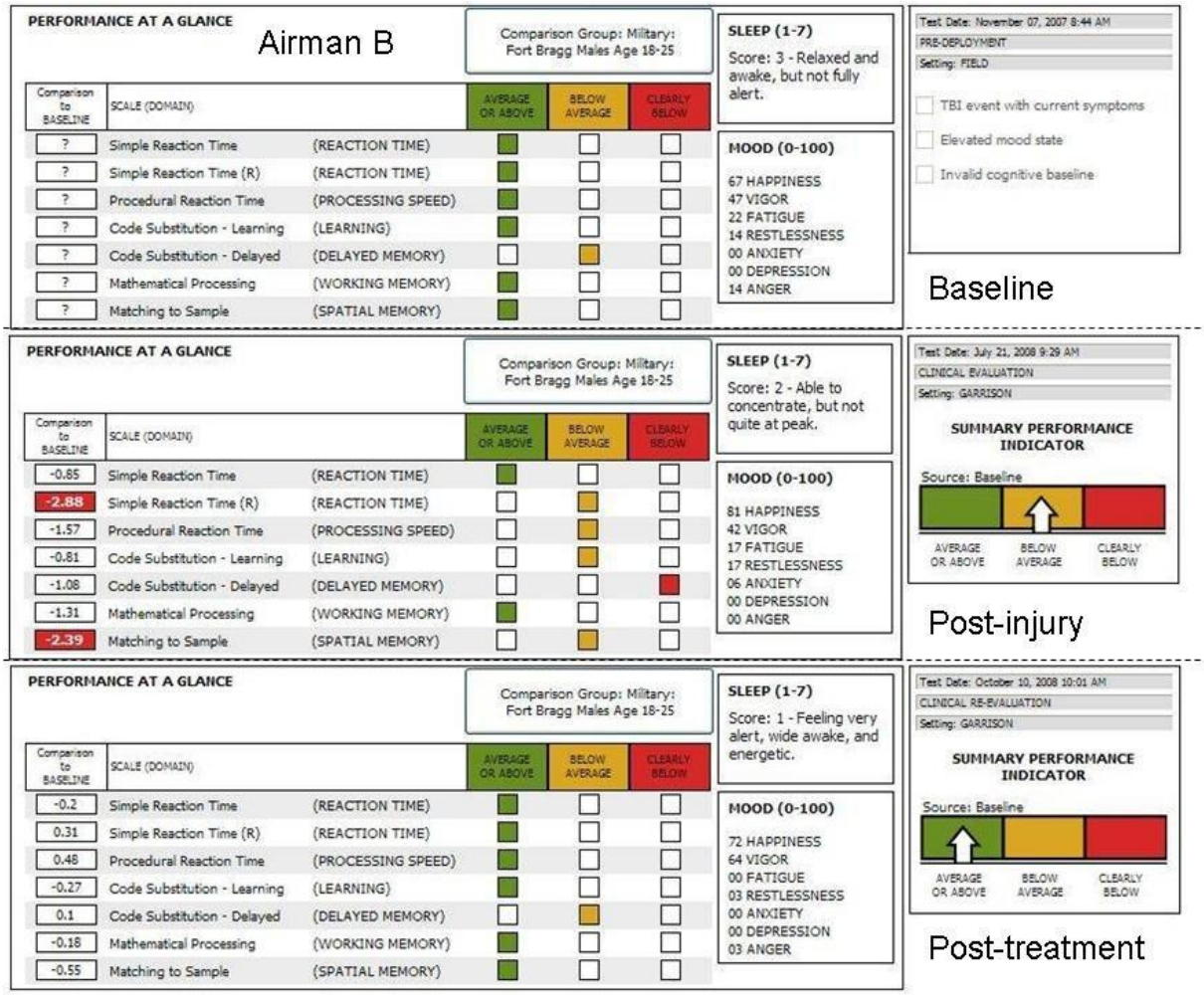

Figure 2a Airman B ANAM scores

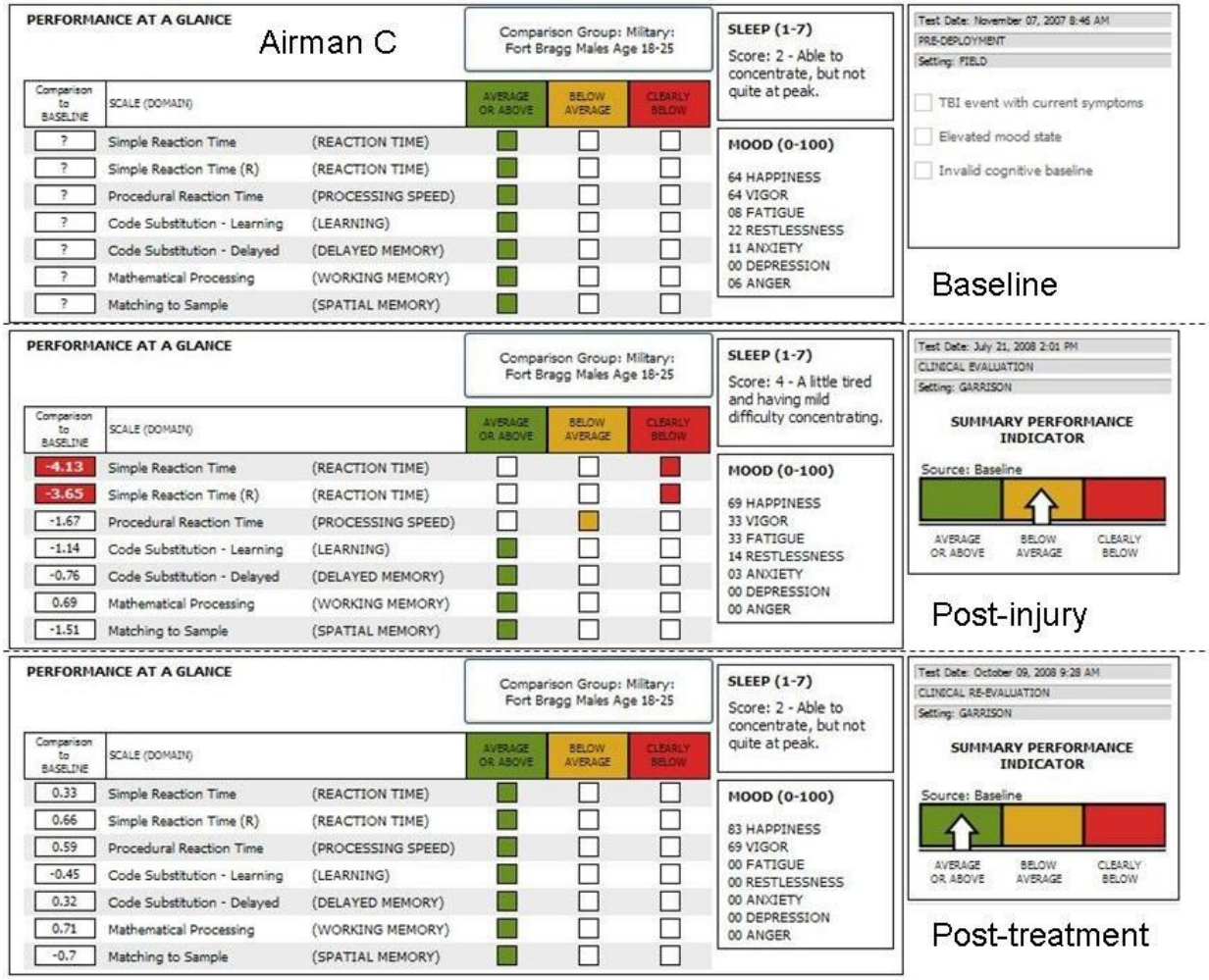

Figure 3b Airman C ANAM scores

Discussion:

Hyperbaric oxygen treatment has several effects that may be beneficial in treating brain injury. In animal models, HBO has been shown to enhance mitochondrial recovery and reduces apoptosis in hypoxic nerve cells[181]. The HBO-induced improvement in mitochondrial function appears to facilitate improved cognitive recovery and reduced hippocampal neuronal cell loss after brain injury[182]. HBO promotes neural stem cell activation and growth[183], and this effect is seen in the hypoxic damaged brain[184]. HBO also alleviates hypoxic-induced myelin damage, and up regulates HIF-1alpha enhancing

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neuronal tolerance to hypoxia, and increases cellular ATP levels and cognitive recovery after concussive injury[185]. Balance beam scores in rats with cerebral contusions were improved after treatment with HBO[186]. In a rat model of chronic TBI, HBO improved spatial learning and increased vascular density in the injured hippocampus[187]. Controlled human studies of the efficacy of HBO after brain injury have been few. In a study of moderate and severe TBI using the Glasgow Coma Scale and Glasgow Outcome Scale as measures of efficacy, an HBO-treated patient showed improvement over controls[188]. HBO has been shown to be clinically effective in mediating the effects of brain injury[189].

ANAM is a library of more than thirty computer-based test modules designed for a wide variety of clinical and research applications and is the direct outgrowth of more than twenty years of computer-based test development across all service branches within the Department of Defense[190]. ANAM4™ is a neurocognitive assessment tool that can be used to identify changes in a service member's cognitive function and mood state as a result of some debilitating event. The ANAM4™ TBI-MIL test battery used in this case report has been tailored to provide an instrument that is sensitive to cognitive changes that often accompany mTBI. The battery consists of a set of assessment modules that gather data on mood, processing speed (reaction time), working memory, short-term memory, spatial pattern recognition/memory, and other cognitive functions. A module is included for reporting exposures, immediate alterations of consciousness, and current symptoms of potential mTBI. The test is designed for repeated testing and is provides reliable measures when used for retesting as a measure of TBI recovery[191]. ANAM is used to establish a cognitive function baseline that can then be used for surveillance post-injury or post suspected injury[192]. The Assistant Secretary of Defense for Health Affairs has directed pre-deployment neurocognitive assessment using ANAM for all deploying Service Members.

The assessment modules and the domains assessed by ANAM4™ TBI-MIL are in sequence as follows:

- Demographics — User Profile
- TBI Questionnaire — TBI History
- Sleepiness Scale — Fatigue
- Mood Scale — Mood State (seven categories of mood)
- Simple Reaction Time — Basic Neural Processing (speed/efficiency with an emphasis on motor activity
- Code Substitution - Learning — Associative Learning (speed/efficiency)

[185] Peng Z, Ren P, Kang Z, Du J, Lian Q, Liu Y, Zhang JH, Sun X. Up-regulated HIF-1alpha is involved in the hypoxic tolerance induced by hyperbaric oxygen preconditioning. Brain Res. 2008; 1212:71–8. Epub 2008 Mar 27.
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[192] Cernich A, Reeves D, Sun W, Bleiberg J. Automated Neuropsychological Assessment Metrics Sports Medicine Battery. Arch Clin Neuropsychol. 2007; 22 Suppl 1:S101–14. Epub 2006 Nov 21.

- Procedural Reaction Time — Processing Speed (choice reaction time/rule following)
- Mathematical Processing — Working Memory
- Matching to Sample — Visual Spatial Memory
- Code Substitution - Delayed — Short-term Memory (delayed memory)
- Simple Reaction Time (R) — Basic Neural Processing (speed/efficiency)

Although not intended as a diagnostic tool per se, comparative performance on ANAM test modules can be helpful in informing the diagnosis as demonstrated in this case report. In cases with known head trauma, computer-based assessments should be supplemented with detailed neuropsychological tests tailored to the patient's presenting problems and to the specific referral question to be answered. This allows for consideration of any sensorimotor limitations, neurobehavioral symptoms, or comorbidities that are not readily assessed by computer-assisted cognitive tests. Although ANAM was sensitive to mTBI in the current circumstances, there may be some patients with brain injury who perform acceptably on the ANAM but are identified using other types of neurological and neuropsychological procedures.

Conclusions:

Several aspects of these two cases demonstrate the efficacy of HBO for the airmen treated. Although both airmen had stable symptoms of mTBI/post-concussive syndrome, which had not improved for seven months; substantive improvement was achieved within ten days of HBO treatment. The headaches and sleep disturbances improved rapidly while the irritability, cognitive defects, and memory difficulties improved more slowly. Fortunately both airman had taken the ANAM and presented objective demonstration of their deficits from TBI and their improvements after HBO treatment. Both airmen, who were injured by the same blast sitting side by side, had similar symptom complexes of TBI and improved at similar rates after initiation of HBO treatment. Neither airman had any other form of treatment for TBI. It seems unlikely to the authors that any explanation other than the HBO treatments can be offered for their improvements.

*720th Special Tactics Group (AFSOC), 223 Cody Ave, Hurlburt Field, FL 32544
**Medical Director, Hyperbaric Medicine Inc., 913 MarWalt Dr, Fort Walton Beach, FL 32547
***Clinical Director, The Anchor Clinic, LLC, 996 Airport Rd, Destin, FL 32541

****Center for the Study of Human Operator Performance (C-SHOP), The University of Oklahoma, 3200 Marshall Ave, Suite 260, Norman, OK 73072

The views in this article are those of the authors and do not reflect the official policy of the Department of the Air Force, the Department of Defense, or the U.S. Government.

APPENDIX III. HBOT in Chronic TBI and TBI with PTSD – Pilot Trial – LSUHSC IRB #7051

2 Groups: 15 with TBI (PCS), 15 with PCS and PTSD
INCLUSION CRITERIA**:** Adult, 18-45 years old; Active duty, non-active duty, or civilian.; One or more mild-moderate TBIs characterized by loss of consciousness due to blast injury that is a minimum of one and maximum of four years old. Diagnosis of chronic TBI/PCS or TBI/PCS/PTSD (military or civilian.) Absence of acute cardiac arrest or hemorrhagic shock at time of TBI.

Protocol:Screening/Testing; Baseline SPECT brain; Single HBOT; Repeat SPECT brain; 39 HBOTs: 1.5 ATA/60 TDT, bid, 5d/wk.; Repeat testing and SPECT; If PBNR < 90%, 1 month break, then; 40 HBOT's: 6/wk.Repeat all above testing; 6 month follow up regarding to return to work or school

Study began in September, 2008.;Complete data on 3 patients by December 5, 2008 DoD Meeting. All three patients with TBI (PCS)/PTSD. All three patients with symptomatic, cognitive, and SPECT improvement. Several additional patients have completed with similar results and additional patients are under treatment now.

Neuropsych Measures	**Pre-Test**	**Post-Test**
• Personal History Q	X	
• *Rivermead PostConcussion Sx Q	X	X
• PTSD CheckList PCL-M	X	X
• 3 Q DVBIC TBI Screening Tool	X	
• Brief Patient's Health Q PHQ-brief	X	X
• Percent-Back-to-Normal Rating	X	X
• Perceived Quality of Life	X	X
• Combat Experience Scale CES	X	
• Michigan Alcohol Screening Test	X	X
• Drug Abuse Screening Test	X	X
• WAIS-IV	X	

	Pre-Test	**Post-Test**
• WASI		X
• Wechsler Test Adult Read WTAR	X	
• Green Word Memory Test	X	
• Rivermead Beh Memory Parag Alt Forms	X	X
• Wechsler Memory Scale-III	X	X
• Rey AVLT-Alternate Forms	X	X
• Stroop Test	X	X
• Grooved Pegboard	X	X
• Finger Tapping Test	X	X
• TOVA	X	X

*Key indicator of Clinical Recovery in TBI Patients

Rivermeade Post-Concussion Symptom Questionnaire –LSU IRB #7051

	Pre	***Post***	***%Δ***
Subject 1:	***40***	***24***	***-40***
Subject 2:	***40***	***35***	***-13***
Subject 3:	***46***	***26***	***-43***
Subject 4:	***27***	***8***	***-70***
Subject 5:	***43***	***31***	***-28***
Average %Δ Improvement			***-37***

This test is the diagnostic test that classifies clinical symptoms in patients who have had concussions (TBI). No treatment other than HBOT 1.5 to date has demonstrated this level of improvement in mild/moderate TBI patients six months post concussion. 64 is the max score. 16 is mild symptoms. A 10% improvement is considered clinically significant. Scores in the 40 range are sufficient to prevent these war casualties from being able to work and interfere with daily life.
This is the same test the "DoD HBOT in TBI" Consensus Conference chose as an indicator of clinical improvement.
Note: All Tests are approximately 35 days apart with 40 HBOT 1.5 1 hour treatments between tests.

Full Scale Intelligence Quotient – LSU IRB #7051

	Pre	***Post***	***%Δ***
	WAIS-IV	***WASI***	
Subject 1:	***104***	***110***	***+6***
Subject 2:	***105***	***129***	***+24***
Subject 3:	***84***	***101***	***+17***
Subject 4:	***100***	***123***	***+23***
Subject 5:	***85***	***100***	***+15***
Average IQ Increase:			***17 IQ Point Increase***

Increase occurs over 35 days.

PTSD Checklist – Military

	Pre	***Post***	***%Δ***
Subject 1:	***48***	***27***	***-44***
Subject 2**:	***65***	***69***	***+06***
Subject 3:	***78***	***42***	***-46***
Subject 4:	***84***	***48***	***-43***
Subject 5:	***68***	***61***	***-10***
Average %Δ Improvement			***-28***

Conclusions regarding LSUHSC IRB Pilot Study #7051 to date.
In the three patients with psychometric testing, the improvements in attention/concentration and memory are consistent with symptomatic improvement in all patients and the image analysis of the corresponding areas of injury/functional neuroanatomy seen in the original cohort. These patient improvements are consistent with recovery of thousands of patients treated with this HBOT 1.5 protocol by scores of physicians over the past 20 years for TBI and other neurological conditions. This data is consistent with data from previous studies.

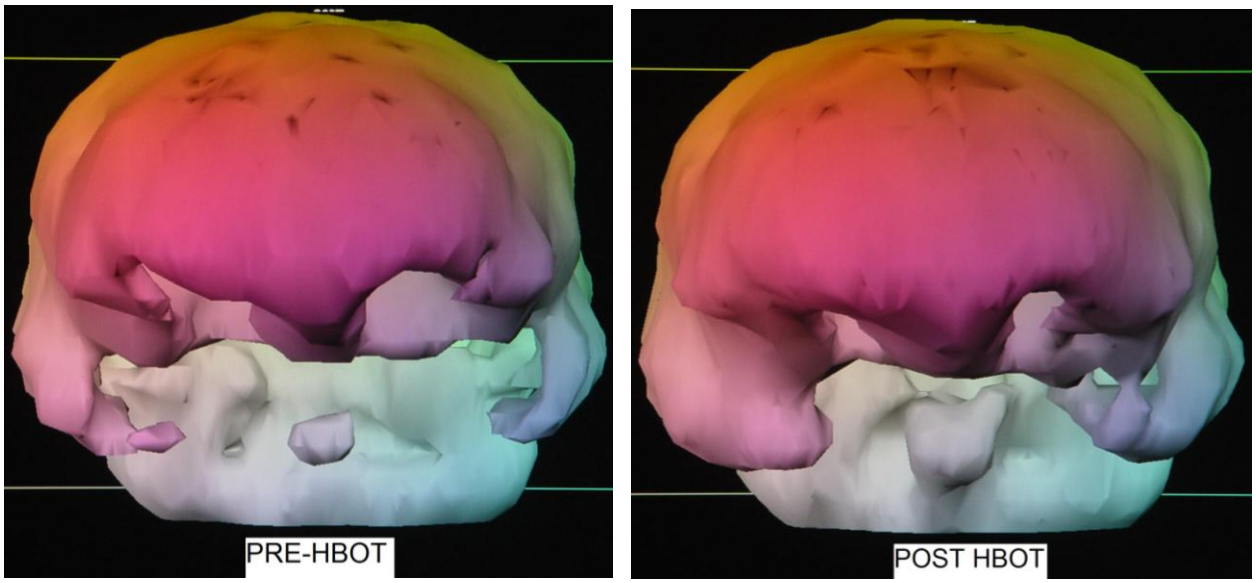
APPENDIX IV. Summary of Five TBI Cases

1) 59 year old Brigadier General. 8/21/05: IED (Improvised Explosive Device) explosion with transient loss of consciousness (LOC), few seconds anterograde memory loss. Affected: nose, herniated disk, headaches, short term memory loss, malaise, fatigue. Medical Evacuation: 10 days later - no memory of flights. Walter Reed: Extensive Evaluation. Cognitive deficits ("low normal" range on psychometric testing).Physical therapy, aqua-therapy, cognitive therapy (beneficial); but still significantly impaired and unemployable.9 months at Walter Reed making no progress with best of DoD Medicine. After 9 months, wife secures HBOT 1.5 information via physician friend in Pensacola, FL who has been using Harch protocol for a several years. HBOT: 9 months post TBI (traumatic brain injury). Harch HBOT 1.5 protocol at George Washington University - 80 HBOTs, 1.5 ata for one hour in two blocks of 40 each. Noticeable improvement at 18 HBOTs. 25 HBOTs: Much more sociable, less napping. 80 HBOTs: significant reduction in back pain, improvement in cognition.**150 days after HBOT 1.5 starts, he leaves Walter Reed returns to the bench as a civilian judge.** Repeat psychometric testing: Improved. Partial regression 6 months post HBOT. Evaluation by Dr. Paul Harch in New Orleans - 11/2007.SPECT brain imaging. Ten additional HBOT treatments in Pensacola, FL. Improved cognitive function. Continues to function as criminal and civil court judge. Films segment on "Medical Breakthroughs." Subject attends meeting with Navy SG on 14 August 2008 to verify these results.

2) 25 year old Humvee Machine Gunner. 3/15/05 IED explosion w/loss of consciousness <1min. 45 minutes anterograde memory loss. Tinnitus, headaches, off-balance, irritability. One month later -2nd IED-"rattled, confused". Two months later-3rd IED-"rattled, confused". Bilateral tinnitus and hearing loss. Nightmares on return to Camp Lejeune. Redeploys: Three more IEDs + rocket propelled grenade -identical to 2nd and 3rd IEDs; "rattled and confused"; Worsened sleep problems, tinnitus, negative attitude/behavior, distrustful, change in personality.

Camp Lejeune: Lost work ethic, reclusive. Months of bureaucratic fighting for hearing aid and various evaluations; became disaffected. Diagnosed with PTSD (10%), TBI(10%), hearing loss (0%). Told: "Live with it, take pills, see a psychologist." Leaves the service. 4/7/08: Evaluated in New Orleans by Dr. Paul Harch. c/o: Headaches, tinnitus, sleep disruption, blurry vision, extreme irritability, marital problems, depression, cognitive deficits. Mild balance findings on physical exam. HBOT and SPECT: 4/7/08 - 5/2/08. 39 HBOTs; 1st HBOT: headaches gone. ; 8th HBOT: sleeping all night-1st time in 3 years.; 12th HBOT: energy up. Tolerates crowds. Goes to French Quarter Festival - 400k people in one day. 25th HBOT: PTSD GONE. 39th HBOT: Most symptoms improved or gone. Tinnitus and blurry vision w/o change. Patient symptoms: improved. Repeat SPECT: Improved. Attends meeting with Navy SG on 14 August 2008 to verify results.

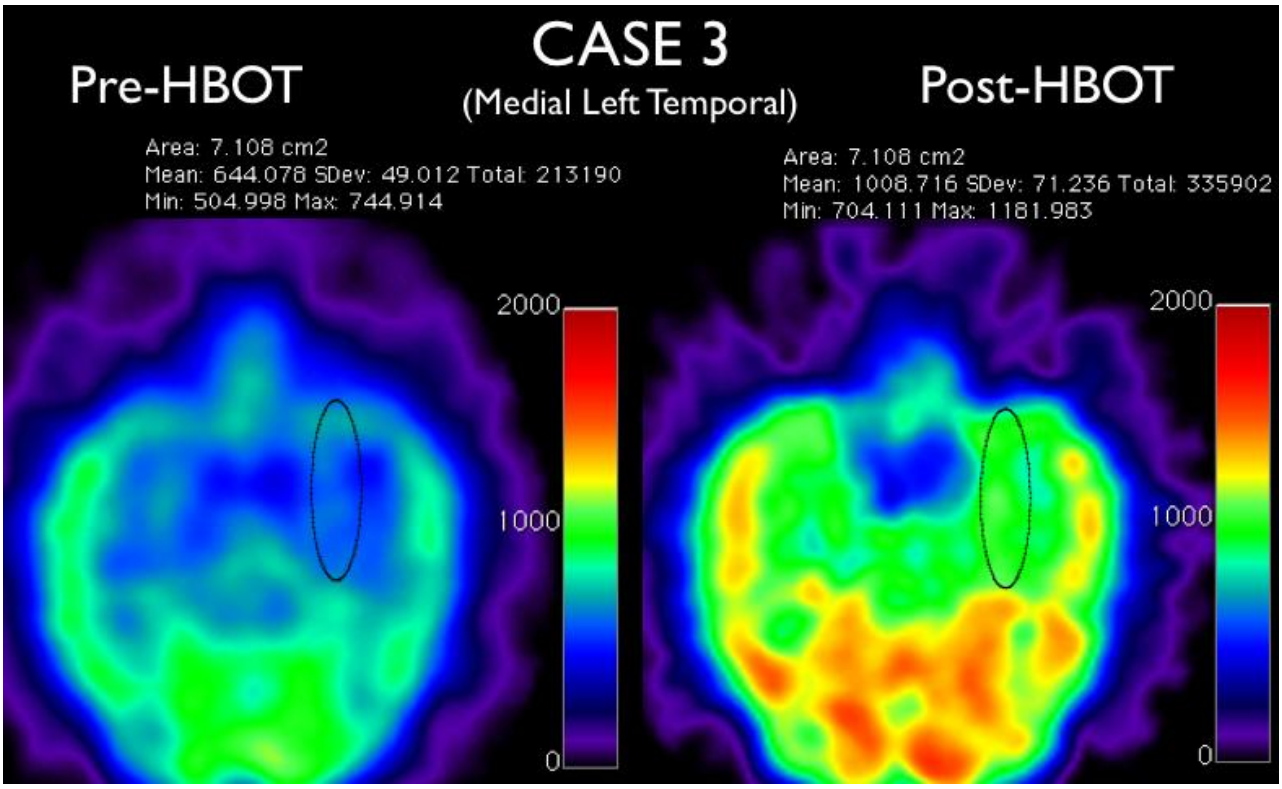
Before and After 40 HBOT 1.5 treatments (1/2 of the Protocol)



HBOT 1.5 Restores Brain Blood Flow & Metabolism

The scale covers a nominal range from 0 to 2000. Those pixels that are approximate 2000 are red and are the most active. The less metabolically active are "cooler" colors of yellow, green and blue. So if you draw a line across the middle of the scale you can see what pixels are registering at 1000 by the corresponding color.

Both pre- and post-HBOT sets of images are exactly on the same scale. Below is a quantitative assessment that shows the actual percent increase in uptake to an area of the brain quite vulnerable to TBI. Note the mean uptake in the area went from 644 to 1008. Similar changes are evident everywhere else; in ballpark numbers, a change from green to red is a doubling of metabolism.



Analysis of blast injured veteran in LSU IRB Study # 7051: Edward Fogarty, MD, Neuro-radiologist, Chair, University of North Dakota School of Medicine, (701) 751-9579.

3) 25 year old Bradley gunner. 5/2003: 1st IED with loss of consciousness for < 1 min. Dizzy, thick-headed, headache, nausea, visual halos. 12/2003: 2nd IED with loss of consciousness for one minute. Back injury. Headache, fatigue, photosensitivity, "silly" in head. Chronic headaches and back pain: starts drinking heavily. No medical evaluations. Honorable discharge. Diagnosis by Veterans Administration: PTSD, depression, personality disorder, L4-5 HNP, mild hearing loss.

6/22/08: Evaluated in New Orleans by Dr. Harch. Complaining of back pain, anger, resentment, memory problems, change in personality, nightmares, paranoia, fatigue, feels crazy. HBOT and SPECT: 6/23 - 7/22/08, 40 HBOTs. Post treatment symptoms: Cognitive function, sleep, fatigue, mood swings, anger now better. PTSD without change. Back pain unchanged, but appeared better. Using 30% less Xanax and markedly less narcotics.

4) 34 year old male. 7/1/07: Simultaneous IEDs (two). Loss of consciousness for a few seconds. Headache, dazed. Later in day: photosensitivity, balance problems, fatigue. Evaluation: concussion. Progressive deterioration: short term memory, multi-tasking, headaches, change in personality, job dysfunction in Iraq. Evaluation at Ft. Rucker. Diagnosis: TBI/PCS (post concussive syndrome) - cognitive deficits, PTSD, migraine and other headaches.

6/25/08: Evaluation in New Orleans by Dr. Harch. Complaining of headaches, cognitive deficits, irritability, sleep dysfunction, depression, foggy-headed. Previous medical history: ~ 9 previous TBIs with loss of consciousness pre-military. Patient symptoms: balance, motor speed, clonus (involuntary muscular contractions due to sudden stretching of the muscle). HBOT and SPECT 6/26-7/31/2008, 37 HBOTs. 10th HBOT: "more clear thinking", increased energy. 12th HBOT: sleeping better. No headaches despite high PTSD (7/4 weekend explosions). 17th HBOT: marked deterioration headaches, fatigue. 31st HBOT: cognitively better. 37th HBOT: migraines less severe, perpetual "fog" gone, improved multi-tasking. Irritability w/o change. Patient symptoms improved. Patient feels 85-90% back to normal (5% improvement overall). Attends meeting with Navy SG on 14 August 2008 to verify results.

5) 39 year old male. 4/2003: large ordnance detonation, no loss of consciousness, but extreme confusion, severe headache and tinnitus. L numbness/balance problems next day. Persistent headaches, short term memory/cognitive problems, progressive work dysfunction. 3/2004: sent home. Headaches, sleep problems, nausea, nightmares, inability to work. 9/2004: Severe headache, N, V, L side weak/numb. CT scan - acute on chronic brain bleed. Surgery to remove cavernous hemangioma (blood clot). Mental confusion worse post surgery. Eventual diagnosis: TBI, PTSD. *3/1/07: double vortex tornado passes over house. House implodes. Severe exacerbation of all symptoms - "felt like after the explosion in Iraq."* Diagnosis: decompression sickness from extreme acute negative depressurization. Severe Obstructive Sleep Apnea diagnosed.

6/25/2008: Evaluated in New Orleans by Dr. Harch. Complains of headaches, short term memory/cognitive problems, imbalance, left side numbness/ weakness, fatigue. Previous medical history: carbon monoxide poisoning with symptoms 1994 and 2002, concussion 1996 (2), 1998 - TBI with loss of consciousness, seizure, brain bleed into hemangioma, 9/2004-rebleed (acute and chronic), 11/2004 - craniotomy/resection. Patient symptoms: photophobic, imbalance, incoordination. HBOT/SPECT: 6/26-7/31/08, 38 HBOTs 1st HBOT: Thinking clearer, no photophobia. Slept 14 hours. 1st time slept more than 2-3 hours in 4 years. 10th HBOT: headaches decreased, more alert, awake, balance better, more energy, no nightmares in more than 1 week. 15th HBOT: lethargy, worse headaches. 17th HBOT: mental capacity improved, energy level up. 20-27th HBOT: global deterioration in symptoms. 32 HBOTs: Global improvement - cognition, clarity of thought, conversation, sleep structure, headaches, reading, no further suicidal thoughts, endurance/ balance/ left side numbness/strength all improved. Has improved from 30% to 70% back to normal. Decreased Lunesta/Percocet, off Provigil. Patient symptoms: Generalized improvement.

After next 40 treatments, patient has returned to duty, had his medical board cancelled, been allowed to reenlist and eligible to be promoted to E-8.

APPENDIX V. HBOT 1.5 Current Score Card

The Results and Costs of Repairing Our War Veterans' TBI & PTSD Injuries
March 28, 2009

HBOT Stats as of 28 March 2009: To date, in the HBOT 1.5 National Brain Injury Rescue & Rehabilitation (N-BIRR) effort, led by Dr. Paul Harch at LSU in New Orleans, 16 combat veterans have been treated by four different members of the N-BIRR team with 15 treated with HBOT 1.5 and one veteran treated for broken vertebrae, off-label, with the wound care protocol HBOT 2.0 for 90 minutes. Veterans have been treated from 35 days to 150 days. All have had improvement in the first 40 treatments. There have been no adverse events and another group of war veterans are in treatment.

Clinical Improvement Status: Each veteran's clinical improvement has been determined through symptom monitoring, independent functional imaging or neuropsychological testing, plus return of executive function. Each of the 16 combat veterans has demonstrated significant clinical improvement and most have had significant improvement or remission of their PTSD symptoms. For those provided with the full battery of neuropsych tests, the results are: Rivermeade Post Concussion Symptom Questionnaire. (Average (Improvement) -37 %Δ. -10% is clinically significant.) PTSD symptoms (Average (Improvement) %Δ = -28, more than clinically significant); Average IQ increase has been 17 IQ points. Most have returned to work.

How HBOT 1.5 Works: Oxygen saturation biologically repairs and causes regeneration of neural tissue and brain structure. HBOT 1.5 is in use at nearly 100 clinics across the nation as standard of care for three kinds of brain insults and – off label – for brain injury injury. Oxygen is used in over 200 cellular processes. While lack of oxygen causes cells to go into a protective, dormant mode to prevent cellular death, hyperbaric oxygen therapy has been shown to reawaken these cells. Unfortunately medical system failures have left this therapy unrecognized for years.

Box Score: Casualties Returned to Active Duty Status: Of the 16 patients, five were still eligible to return to duty after treatment. We are pleased that all five have returned to duty. (The other 11 individuals had already been medically boarded out, or otherwise ended their military obligation.) One of the five veterans returned to Iraq after treatment and received a Silver Star. He had been freshly injured in the line of duty and on a path to be boarded out of the service before he received off-label HBOT 2.0 treatments for fractured vertebrae and nerve damage from the N-BIRR team. He is testified to Congress March, 26th.

Treatment Success By Service: Breakout of HBOT 1.5 Treatments			
Air Force	**Army**	**Marines**	**Navy**
Casualties 3	5	7	1*
Colonel Wright, MD (Eddie Zant, MD) (3)	Paul Harch (3)	Paul Harch (7)	Kraig Dorner, USN, Ret (San Diego, CA)

	Walter Reed DC (1)		* Off-Label Wound
	Ken Stoller NM (1)		Care Protocol HBOT 2.0

Retention Benefit Update: In the first discussion of the HBOT 1.5 treatment for brain injury and PTSD with ADM Walsh, Vice Chief of Naval Operations, last June 5th, his main concern was how many of his injured veterans could be retained in the service and put back to work. Here is the score thus far.

As of 27 January 2009 – 5 confirmed and 2 potential as detailed below

HBOT Retention Benefit Status			
Air Force	**Army**	**Marines**	**Navy**
3	1	0 (2 treated)	1

Costs of Replacing Trained War Veterans

It costs $20,000 to recruit a new member of the Armed Forces and $35,000 to send them to basic training. Further costs have been incurred to prepare them for combat operations ($100,000 to $150,000), send them through leadership schools, and increase their military skills. SOCOM (Special Forces, SEALS, etc.) cost hundreds of thousands more to train. How much is a senior NCO with 20 years of experience worth, or specialized veterans with technical expertise?

Medicare's payment, on average would be $16,000 if TBI/PTSD treatments were reimbursed. This covers treatments over 150 days with 80 HBOT 1.5 treatments. It costs far less for the military to treat their own injured service members (about $800 per patient for the oxygen.) An airplane pilot costs $5 million to train. Dr. Zant just treated a STO (Special Tactics Officer) whose training costs as much as a pilot. Returning the Naval Academy Graduate SEAL team member, who received a silver star, to duty saved the Federal government far more than $1 million. Not paying the provider the $7,500 owed for the HBOT 2.0 wound care treatment that enabled him to return to Iraq seems short-sighted, particularly so in view of the number of TBI casualties still in the service, many of whom would like to continue to serve.

Recruiting and retention goals in the volunteer armed services have further been hampered by wide publicity associated with untreated casualties returning from theater and being unable to function. Law enforcement, usually a ready source of employment for veterans, has been refusing to hire them because of TBI & PTSD associated with numerous news reports and adverse experience with this veteran population.

HBOT Retention Savings (Replacement Cost) to Gov't vs Cost of Treatment			
Air Force	**Army**	**Marines**	**Navy**
3 2 Airmen: $155,000 ea 1 STO: $5 million	1 E-7(P) Helicopter	0 (2 potential in treatment now)	1 Naval Academy Graduate SEAL
Replacement Costs $5.03 mil	$596,000	($150,000*2=$300,000)	Cost Savings: $706,000

Note: Replacement Costs are Training Costs & Do Not take into account years of service or econometrics of how many Navy personnel, for example, need to be trained to field one qualified SEAL, let alone an E-7 with 20 years of service or qualified Marine or a General officer. [Those metrics will be used as acquired.] Estimates also do not account for the amount to be spent in the future on training a replacement, the cost of replacement of combat experience (priceless), future lost job performance & combat impact, disability payments for life due to unnecessary & premature medical boarding/retirement, & personal, family, & societal costs of the long-term ramifications of untreated TBI & PTSD: unemployment, substance abuse, spousal & child abuse, petty crimes, prison sentences for a range of crimes of violence, & suicide.			
Unreimbursed Treatment Cost: Zant $35,000	Harch: $20,000	(Harch: $40,000)	Dorner: $7,500

Savings to the Gov't: $6.3 million. Medical Treatment Costs Unreimbursed: $62,500. It is hoped with these demonstrated results, policy makers can find a pathway for HBOT 1.5 reimbursement for those who have recovery. When a treatment consistently restores these casualties to work or duty, it should be fostered and is unlikely to be found a placebo. HBOT itself is paid for by Tricare and VA for 13 other approved indications and is well known to heal non-healing wounds. This therapy is available now and hundreds of casualties could be treated each day. This would restore most of them to functional lives and save millions.

Paul G. Harch M.D., LSU Hyperbaric Medicine Fellowship Director
Dr. William A. Duncan, Capitol Strategy Consultants (below)
Martin R. Hoffmann, Esq., Secretary, U.S. Army (1975 to 1977)

APPENDIX VI. Safety of HBOT 1.5 in the 35,000 pediatric cases

LOW PRESSURE HYPERBARIC OXYGEN THERAPY FOR PEDIATRIC BRAIN INJURY, A MINIMAL RISK MEDICAL TREATMENT

Paul G. Harch, M.D., Jamie Deckoff-Jones, M.D., Richard A. Neubauer, M.D., Hyperbaric Medicine Physicians See authors' affiliations at end of article. Pediatrics Online, 12 Feb 2001 [Response]

LOW PRESSURE HYPERBARIC OXYGEN THERAPY FOR PEDIATRIC BRAIN INJURY, A MINIMAL RISK MEDICAL TREATMENT 12 February 2001 Paul G. Harch, M.D., Jamie Deckoff-Jones, M.D., Richard A. Neubauer, M.D., Hyperbaric Medicine Physicians

LOW PRESSURE HYPERBARIC OXYGEN THERAPY FOR PEDIATRIC BRAIN INJURY, A MINIMAL RISK MEDICAL TREATMENT RESPONSE TO NUTHALL ARTICLE

Dear Sirs:
We read the recent contribution to your esteemed journal by Nuthall, et al with extreme disappointment. Unfortunately, this article distorts the true complication rate of low-pressure hyperbaric oxygen therapy (LPHBOT) in the treatment of pediatric neurological conditions. Noticeably missing from the paper is an estimate of the frequency with which these complications occur. Without such perspective, this article misleads the medical community and fuels the unfounded fear that LPHBOT is dangerous for children with cerebral palsy, when in fact it is both safe and an extremely useful adjunctive therapy.

The first case mentioned in the article, vomiting with aspiration, is a complication that can occur in an adult or pediatric patient with gastro esophageal reflux in many medical settings, hyperbaric or normobaric. Unfortunately, the article does not give enough information for a critical appraisal of the patient's care. Air swallowing at anytime, but especially during and HBO treatment, can lead to gastric distention, which can worsen, on ascent. It is easily avoided by simple venting in patients with feeding tubes. The "tight-fitting" oxygen hood implies neck constriction, but the hood used in multiplace chambers throughout the United States and Canada in fact utilizes a comfortably fitting latex neck dam. A competent attendant can easily remove the hood if needed and suction should be available in the chamber. Aspiration is a rare complication of HBOT, but does occur in the ill adult population. To put the matter in perspective in the pediatric population, since the first HBOT for a CP child in North America in 1992 (2) authors PGH and RAN have logged over 35,000 treatments on brain-injured children without a single case of primary aspiration or air embolism. Approximately 7,000 of these treatments were performed on an IRB-approved protocol. The point is that this case report represents a very rare indeed, and most likely a completely avoidable one in a setting of adequate care. We believe the slight risk is acceptable given the positive responses in the vast majority children treated.

The second case is an unfortunate example of an acutely ill child who should have been denied treatment by proper pre-treatment evaluation the day of the accident. The authors attribute the child's cerebral infarct to an oxygen embolism caused by primary arterial bubbles during decompression or venous oxygen bubbles breaching the pulmonary filter or a patent foramen ovale (PFO). In our opinion, this diagnosis is exceedingly unlikely, the mechanisms suggested by the authors nearly impossible to account for their diagnosis, and their argument not supported by the references cited. Primary arterial bubbles of any gas are only seen in explosive decompressions (3). No such scenario is described in the article.

Primary venous bubbles occur in almost all decompressions, but oxygen decompression sickness, and presumably bubbles, have only been documented in animals at 3.53 atmospheres absolute (ATA) of oxygen (4) which is over two times the oxygen exposure of this patient. Furthermore, venous bubbles of any gas will form in proportion to the gas load of the dive. This patient's dive, 1.5 ATA, is a very shallow exposure, which would produce minimal, or no bubbles. Venous bubbles that do form during decompression have been measured to be mostly 19 to 180 microns with some larger bubbles up to 700 microns (5). While it is possible for the bubbles to breach insulted lungs (Para influenza induced respiratory failure) or proceed through a PFO to cause an infarct they would have to selectively coalesce and be retained in the much larger MCA. This is highly unlikely, given the argument above and the fact that oxygen bubbles should be readily metabolized, and hence transient.

Lastly, the two references cited to justify two of the proposed mechanisms don't apply this case; both are articles on iatrogenic air embolism (6, 7) and/or pulmonary barotrauma (6). In addition, the Muth article (6) contradicts the authors' mechanisms by stating, "Cerebral arterial gas embolization typically involves the migration of gas to small arteries (average diameter, 30 to 60 microns)." The MCA is much larger in a 10-month-old child. Muth further states that all

patients with clinical symptoms of arterial gas embolism should receive recompression treatment with hyperbaric oxygen. To attribute this child's cerebral infarct to an oxygen embolism by any mechanism is nearly impossible. More likely, this infarct was the result of a vasospastic event, fat embolism from infected marrow, or some other etiology related to the child's concurrent infection.

Patient safety is paramount and we believe that physician attended HBOT is mandatory.

The Nuthall article begs the greater question of why patients are driven to non-physician attended facilities to obtain medical treatment. The British Columbia College of Physicians and Surgeons (8) and an ex-president of the Undersea and Hyperbaric Medical Society (UHMS) purportedly speaking for the UHMS (9) have now forbidden and threatened doctors, respectively, should they treat non-UHMS approved pediatric neurological disease with HBOT. This is a dangerous and intolerable precedent. Off-label use of any FDA approved device or drug by a qualified ethical physician constitutes the legal practice of medicine. It is to the medical professions embarrassment that families are forced to seek care from facilities, which may be ill equipped or staffed by personnel who lack medical training.

The call for a randomized controlled trial, while desired, strikes a loud and clear double standard. There exists far more evidence to support cerebral palsy as a UHMS HBOT "accepted indication"(10) than existed for cerebral abscess, the last indication added to the list in 1996. In addition, reviews of the accepted indications list by author PGH in 1998 for a presentation at the Advanced Topics Course in Hyperbaric Medicine (11), by evaluators for the Calgary Regional Health Authority in 1999 (12), and Blue Cross/Blue Shield in 2000 (13) found that as many as 6 -7 of the accepted thirteen diagnoses are not supported by either controlled clinical trials and/or adequate research. The statement by the Nuthall article that neither they nor the UHMS can recommend HBOT for CP in the absence of randomized (Nuthall) controlled (UHMS and Nuthall) clinical trials is inconsistent.

In conclusion, we must correct the Nuthall article's frightening implication and inform the medical community that low-pressure HBOT for pediatric brain injury is a very low risk medical treatment, supported by our combined experience of greater than 35,000 patient treatments.

Thank you,

Paul G. Harch, M.D.
Hyperbaric Medicine Fellowship Director
Clinical Assistant Professor
Department of Medicine
Section of Emergency and Hyperbaric Medicine
LSU School of Medicine
New Orleans, Louisiana

Jamie Deckoff-Jones, M.D.
New England Hyperbaric Center
Great Barrington, Massachusetts

Richard A. Neubauer. M.D.
Ocean Hyperbaric Center
Lauderdale-by-the-Sea, Florida

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