Module III: Frontiers in Neurology and Brain Health

Live virtual platform
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Hyperbaric Oxygen Therapy for Mild Traumatic Brain Injury/ Persistent Postconcussion Syndrome

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Possible Conflict of Interest:
Owner/president of Harch Hyperbarics, Inc.,
A corporation which offers consulting and expert opinions.

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All of the material in this lecture pertaining to and derived from Dr. Harch's practice and research is derived from the practice of medicine since 371 B.C., the year of Hippocrates' death, and is according to the Hippocratic Oath, known in the U.S. since the 1938 Food, Drug, and Cosmetics Act and the 1976 Medical Device Amendments as the Off-Label Practice of Medicine

Learning Objectives

1. To understand that hyperbaric oxygen therapy is a dual-component therapy consisting of increased pressure and hyperoxia with primary effects on modulation of anti-inflammatory gene expression and pro-inflammatory gene suppression.

2. To understand that the secondary injury that dominates TBI is largely mediated by inflammation.

3. To understand that multiple (RCTs) randomized controlled trials demonstrate efficacy of HBOT in mild TBI/persistent postconcussion syndrome (PPCS) with or without PTSD and this body of literature now constitutes evidence-based medicine for HBOT in mTBI/PPCS.

Outline

1. Brief review of HBOT
2. Brief review of TBI
3. FDA drug and device proofing/approval process (old standard)
4. Historical review of author's experience with HBOT in chronic TBI
   A. Louisiana divers.
   B. Louisiana boxers. (CTE).
   C. Case series.
   D. Animal study of chronic severe and mTBI.
   E. Pro bono U.S. war veterans (continues to this day).
   F. Case-controlled study of HBOT in mTBI/PPCS + PTSD.
   G. "Act of Congress:" funding for HBOT mTBI/PPCS RCT.
5. Harch-Andrews LSU RCT
6. Comparison to other mTBI/PPCS studies.
7. Making Sense of the studies: interpretation in terms of and reinforcement of scientific definition of HBOT. Placebo argument in 2012 LSU Pilot Trial. "Ritual."
8. Satisfying the FDA recommendation of 2011.
9. Conclusion and recommendation for government and insurance reimbursement. Class A, American Heart Level 1.

WHAT IS HYPERBARIC OXYGEN THERAPY?

For five decades the hyperbaric field has relied on one version or another of this definition

TRADITIONAL DEFINITION:

"Hyperbaric oxygen (HBO_2) treatment, in which a patient *breathes* 100% oxygen intermittently while inside a treatment chamber at a pressure higher than sea level pressure (i.e., > 1 atmosphere absolute: ATA), can be viewed as the new application of an old established technology to help resolve certain recalcitrant, expensive, or otherwise hopeless medical problems…pressurization should be at 1.4 atmospheres or higher."

UHMS HBOT Committee Report, 1999

HBOT
"Accepted Indications"

1. Air or Gas Embolism — Acute Wd
2. CO Poisoning/Smoke Inhalation — Acute Wd
3. Clostridial Myonecrosis (gas gangrene) — Acute Wd
4. Crush Injury, Compartment Syndrome, and other acute Traumatic Ischemias — Acute Wd
5. Decompression Sickness — Acute Wd
6. Selected Problem Wounds (diabetic, arterial insufficiency, venous stasis, etc.) — Chronic Wd
7. Exceptional Blood Loss (Anemia) — Acute Wd

UHMS HBOT Committee Report, 20014

HBOT
"Accepted Indications"

8. Necrotizing Soft Tissue Infections	Acute Wd
9. Osteomyelitis (Refractory) or (Acute) in Compromised Hosts	Chronic, Acute Wd
10. Radiation Tissue Damage (Osteoradionecrosis and Soft Tissue)	Chronic Wd
11. Skin Grafts and Flaps (Compromised)	Acute Wd
12. Thermal Burns	Acute Wd
13. Intracranial Abscess	Acute Wd
14. Central Retinal Artery Occlusion	Acute Wd
15. ISSHL	Acute/Subacute Wd

UHMS HBOT Committee Report, 2008

Historical Definition-What's good about it?

1. It became the foundation for a field of medicine whose scientific underpinnings were poorly understood.
2. It enabled the reimbursement of hyperbaric therapy by defining the methodology by which reimbursement would be secured, i.e., tying reimbursement to recommendations of "certain" diagnoses that were determined by "authoritative" sources.
3. By enabling reimbursement it legitimized and established the credibility of hyperbaric medicine .

However, it is time to admit that this definition is scientifically inadequate.

Historical Definition-What's wrong with it?

1. We have a treatment defined by the diseases it treats. Odd. (antibiotic therapy is not defined by pneumonia).

2. The word "certain" is a major problem. The definition is dependent on a list of diagnoses determined by a group of doctors.
   a. That has worked for reimbursement in the U.S.
   b. What happens when you cross country borders? (70+ diagnoses in Russia, 40+ in China, 30+ in Japan, etc.)
      i. Science doesn't change at country borders. Does Newton's apple fall the same way in Russia, China, and Japan as it does in the U.S?
      ii. A scientific definition should be independent of country borders.

3. The definition says it is 100% oxygen at greater than 1 ATA, but then contradicts itself and states a threshold dose for HBOT, >1.4 ATA.
   a. There is no scientific evidence that HBOT is 1.4 ATA and 1.399 HBOT is not.

4. It assumes that HBOT is exclusively the biology of hyperoxia.

A Scientific Definition of HBOT

1. In 1998 Dr Richard Neubauer and I proposed a new definition of HBOT:

Hyperbaric oxygen therapy is the use of greater than atmospheric pressure oxygen as a drug to treat basic pathophysiologic processes.

This was edited to:

"…we define HBO as a medical treatment that uses high pressure oxygen as a drug by fully enclosing a person or animal in a pressure vessel and then adjusting the dose of the drug to treat pathophysiologic processes of the diseases. "[1]

(i.e., HBOT is the physiology and biology of hyperbaric hyperoxia)

1. Harch PG, Neubauer RA. Chapter 18, in The Textbook of Hyperbaric Medicine, 3rd Edition. Ed. K.K. Jain, Hogrefe and Huber Publishers, Gottingen, Germany, 1999.

Further Refinement of the Definition of Hyperbaric Oxygen Therapy

- Fall, 2010: Special Protocol Assessment Request to the FDA for RCT on HBOT in mTBI/PPCS.
- Application for HBOT 1.5 ATA vs. control group.
- Multi-center: LSU and Oklahoma State University
- Declined with recommendations:

Further Refinement of the Definition of Hyperbaric Oxygen Therapy

"We consider your intervention (hyperbaric oxygen therapy) to be a combination therapy, the constituents of which are hyperbaric treatment and hyperoxic treatment. Each of these constituents has the potential to contribute independently to the overall therapeutic effect."

Further Refinement of the Definition of Hyperbaric Oxygen Therapy

What?

In 24 years of clinical hyperbaric medicine upto 2010, nowhere at any time has there been any discussion or information on the biological activity of pressure.

So, when the going gets tough…

the tough…….. go to the library!

Further Refinement of the Definition of Hyperbaric Oxygen Therapy

Literature search on the biological effects of pressure:

Since the 1940s there are dozens of articles on the physiologic/biologic effects of pressure, including micropressure.

Became the foundation for the J of Neurotrauma and Undersea/Hyperbaric Medicine Letters to the Editor regarding the Wolf, et al, and Weaver, et al articles.

HARCH, PAUL G. HYPERBARIC OXYGEN THERAPY FOR POST-CONCUSSION SYNDROME: CONTRADICTORY CONCLUSIONS FROM A STUDY MISCHARACTERIZED AS SHAM-CONTROLLED. JOURNAL OF NEUROTRAUMA,2013;30:1995-1999.

Further Refinement of the Definition of Hyperbaric Oxygen Therapy

Micropressures of 1.0015-1.3 ATA

ELSEVIER

Comparative Biochemistry and Physiology Part A 122 (1999) 13–36

CBP

Review

The transduction of very small hydrostatic pressures

A.G. Macdonald [a,*], P.J. Fraser [b]

[a] *Department of Biomedical Sciences, Zoology Building, Tillydrone Avenue, University of Aberdeen, Aberdeen AB24 2TZ, Scotland, UK*
[b] *Department of Zoology, Tillydrone Avenue, University of Aberdeen, Aberdeen AB24 2TZ, Scotland, UK*

Received 17 July 1998; accepted 23 November 1998

Physiologic Effects of Increased Hydrostatic Pressure

"Pressures from 1.21–1.26 ATA delivered to human[29–31] and 1.0015–1.015 ATA to animal endothelial cells,[32] and 1.10 and 1.20 ATA to human platelets[33,34] for 15 min or longer have caused the elaboration or suppression of vasoactive substances,[29–31] and the elaboration of growth factors,[32] inflammatory mediators,[33] oxidation products,[34] and cell proliferation.[32] This literature and biological effects from a 1-min exposure to 1.09 ATA or 3 min at 1.04 ATA[17] inform the symptomatic improvements noted in the Wolf and associates[1] ''sham'' group, as do benefits of hyperbaric air on spinal function and PTSD in spinal cord injured veterans during a SCUBA diving training course.[28]

Harch, P.G. Letter to the Editor, J of Neurotrauma, submitted 12/2012

REMINDER

The entire history of hyperbaric medicine from its origin in 1664 to the 1950s was the use of compressed air at pressures upto 3 ATA? for both acute (Spanish Flu, renal failure, etc.) and chronic conditions.[1]

In 1887 Arntzenius published a review article on hyperbaric therapy with 300 references.[2]

1.Vance Trimble, The Uncertain Miracle, Random House, 1973.
2.Jain KK. Chapter 1, Textbook of Hyperbaric Medicine, 1st Edition, 1996

Physiologic/Scientific Definition of HBOT

Hyperbaric Oxygen Therapy is the (pharmacologic) use of greater than atmospheric barometric pressure and oxygen as drugs to treat basic disease processes/states (pathophysiology), and their diseases.

Harch, PG. Textbook of Hyperbaric Medicine, 6th Ed, Chapter 20, 2017.

Primary mechanism of action of HBOT?

Modulation of gene expression and suppression

(gene therapy)

HBOT and Gene Effects

Godman CA. Cell Stress and Chaperones, DOI 10.1007/s12192-009-0159-0 (Courtesy Dr. Philip James)

Human microvascular endothelial cells, in vitro
1st HBOT: 2.4 ATA/60 mins; 2nd HBOT at 24h
Continuous mass gene analysis for 48h

Results:

At 24h:

1. 8,101 genes of the ~19,000 human protein-coding genes were up or down regulated compared to control

At 48h:

1. Cells formed microtubules (blood vessels) in a petri dish

Anti-inflammatory Genomic Effects of HBOT

Godman CA. Cell Stress and Chaperones, DOI 10.1007/s12192-009-0159-0 (Courtesy Dr. Philip James)

1. Largest clusters of genes upregulated:: anti-inflammatory and growth/repair hormones genes.
2. Largest clusters of genes downregulated: pro-inflammatory and cell death genes.

Anti-inflammatory Genomic Effects of HBOT

UHM 2013, VOL. 40, NO. 2 – INFLAMMATORY GENE EXPRESSION ALTERED BY HBO_2 PRESSURE

Different oxygen treatment pressures alter inflammatory gene expression in human endothelial cells

Alexandra C. Kendall [1,2], Jacqueline L. Whatmore [1], Lorna W. Harries [1], Paul G. Winyard [1], Paul Eggleton [1,3], Gary R. Smerdon [2]

Human umbilical vein endothelial cells (HUVEC) Hyperbaric oxygen therapy down-regulates multiple inflammatory and apoptotic genes

Kendall, A.C., et al. Undersea Hyper Med, 2013;40(2):115-123

Anti-inflammatory Genomic Effects of HBOT

Neurochem Res (2009) 34:1047–1056
DOI 10.1007/s11064-008-9873-8

ORIGINAL PAPER

Microarray Analysis of Gene Expression in Rat Cortical Neurons Exposed to Hyperbaric Air and Oxygen

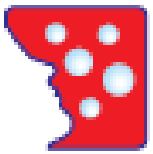
Ye Chen · N. Suzan Nadi · Mikulas Chavko · Charles R. Auker · Richard M. McCarron

Rat cortical neurons:
Hyperbaric oxygen therapy up-reglates neuro-protective and anti-oxidant genes

Chen, Y., et al. Neurochem Res, 2009;34:1047-1056

Anti-inflammatory Effects of HBOT-Review

Rossignol *Medical Gas Research* 2012, 2:6
http://www.medicalgasresearch.com/content/2/1/6



MEDICAL GAS RESEARCH

REVIEW Open Access

Hyperbaric oxygen treatment for inflammatory bowel disease: a systematic review and analysis

Daniel A Rossignol

"HBOT has been shown to possess potent anti-inflammatory properties in both animal (55,67,68) and human (10,11,20,46,69) studies and has been reported to decrease the production of pro-inflammatory cytokines….in both animal (66,70) and human (20,49) studies as well as increase IL-10 levels (71)."

Anti-inflammatory Effects of HBOT-Review

Review Article
TheScientificWorldJOURNAL (2006) 6, 425–441
ISSN 1537-744X; DOI 10.1100/tsw.2006.78

TheScientificWorldJOURNAL
www.thescientificworld.com

Effects of Hyperbaric Oxygen on Inflammatory Response to Wound and Trauma: Possible Mechanism of Action

Noori S. Al-Waili* and Glenn J. Butler
Life Support Technologies, Inc. – New Technologies, Inc., Chronic Wound Treatment and Hyperbaric Medicine Center, The Mount Vernon Hospital, 7th Avenue 12 North, Mount Vernon, NY 10550

"HBO_2 has important effects on the biology of cytokines and other mediators of inflammation. HBO_2 causes cytokine down-regulation and growth factor upregulation, transiently suppresses stimulus-induced proinflammatory cytokine production, affects the liberation of TNF alpha and endothelins, and reduces PGE2 and COX-2 mRNA

Medical Definition of Sham and Placebo

Sham:

"being a treatment or procedure that is performed as a control and that is similar to but omits a key therapeutic element of the treatment or procedure under investigation."[1,3]

The key therapeutic elements of hyperbaric oxygen therapy are increased pressure and hyperoxia.

Placebo:
"An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug."[2,3]

Based on these definitions and the scientific definition of HBOT a sham hyperbaric treatment can have no increased pressure and no hyperoxia.

1. https://www.merriam-webster.com/dictionary/sham#medicalDictionary
2. https://www.thefreedictionary.com/placebo
3. Harch, PG. J Neurotrauma, 2013;30:1995-9.

Shift Gears

http://hdimge.com/post/pink-beach-sunset-for-desktop-background-13-high-definition-wallpaper.html

TRAUMATIC BRAIN INJURY DEFINITION

Traumatic brain injury (TBI) is a nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness.

http://emedicine.medscape.com/article/326510-overview

TRAUMATIC BRAIN INJURY CLASSIFICATION

Classification of TBI Severity
US VA/DoD ibid

Criteria	Mild	Moderate	Severe
Structural imaging [CT/MRI]	Normal	Normal or abnormal	Normal or abnormal
LOC	0–30 min	> 30 min and < 24 hours	> 24 hrs
AOC	a moment up to 24 hrs	> 24 hours. Severity based on other criteria	> 24 hours. Severity based on other criteria
Duration of PTA	< 24 hrs	24 hrs to < 7 day	7 days or more
GCS	13 to 15	9 to 12	3 to 8

https://www.slideshare.net/leishmanassociates/management-of-traumatic-brain-injury-wallace-5722741

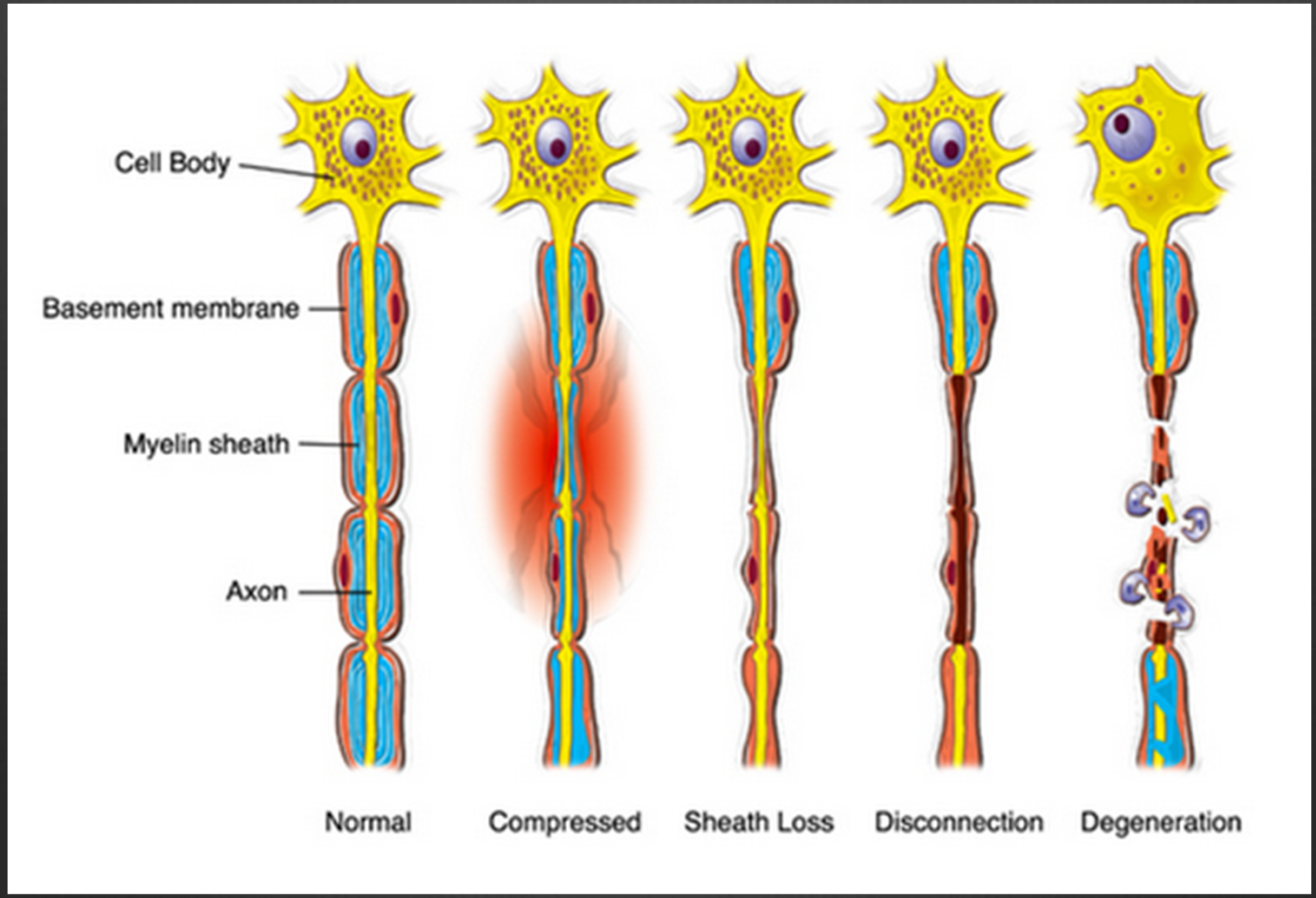
TRAUMATIC BRAIN INJURY PATHOLOGY

Primary Injury:

1.Acceleration/deceleration with shear, stretch, compression, tearing of white matter.

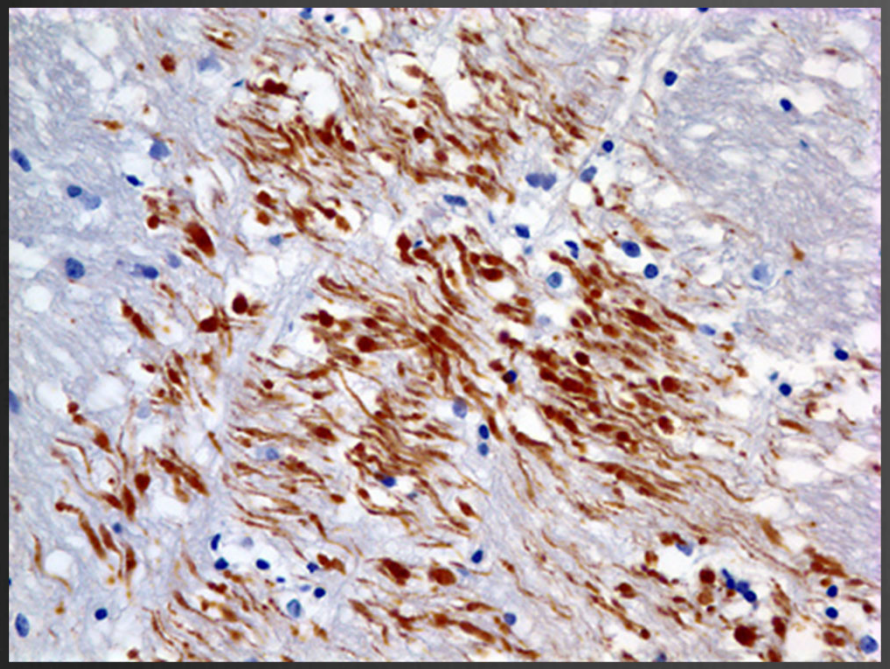
2. Secondary Injury: the inflammatory reaction, biochemical and neurotransmitter storm

Axon Injury



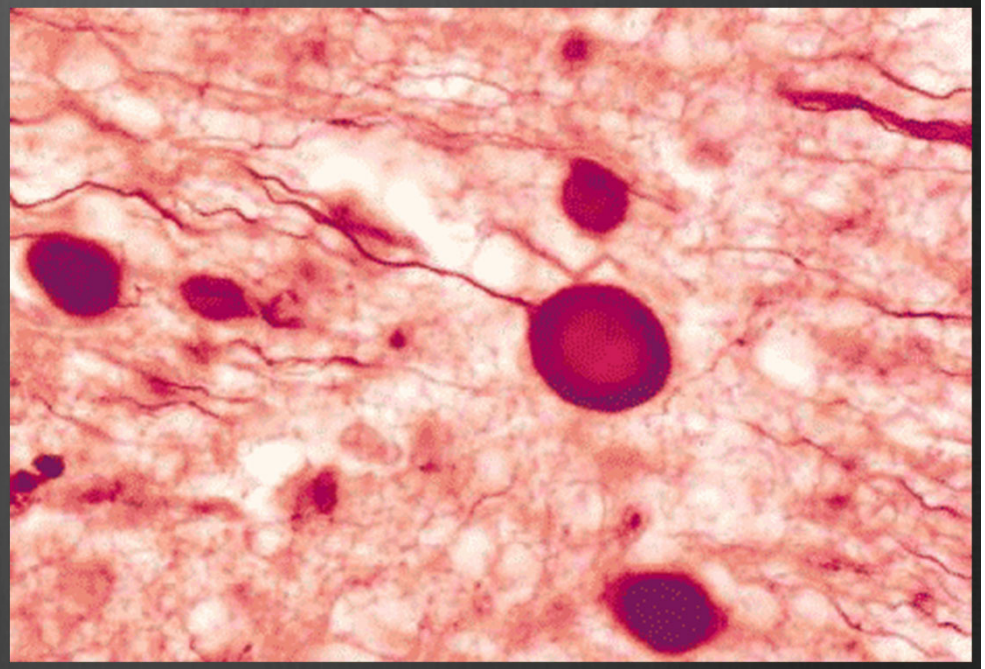
http://imueos.blogspot.com/2010/11/degeneration-regeneration-of-peripheral.html

Diffuse Axonal Injury



Diffuse axonal swelling (brown)

http://neuropathology-web.org/chapter4/chapter4bContusions_dai_sbs.html



Axon contraction balls

http://moon.ouhsc.edu/kfung/JTY1/NeuroSim/Sim05-B-Diss-4-a.htm

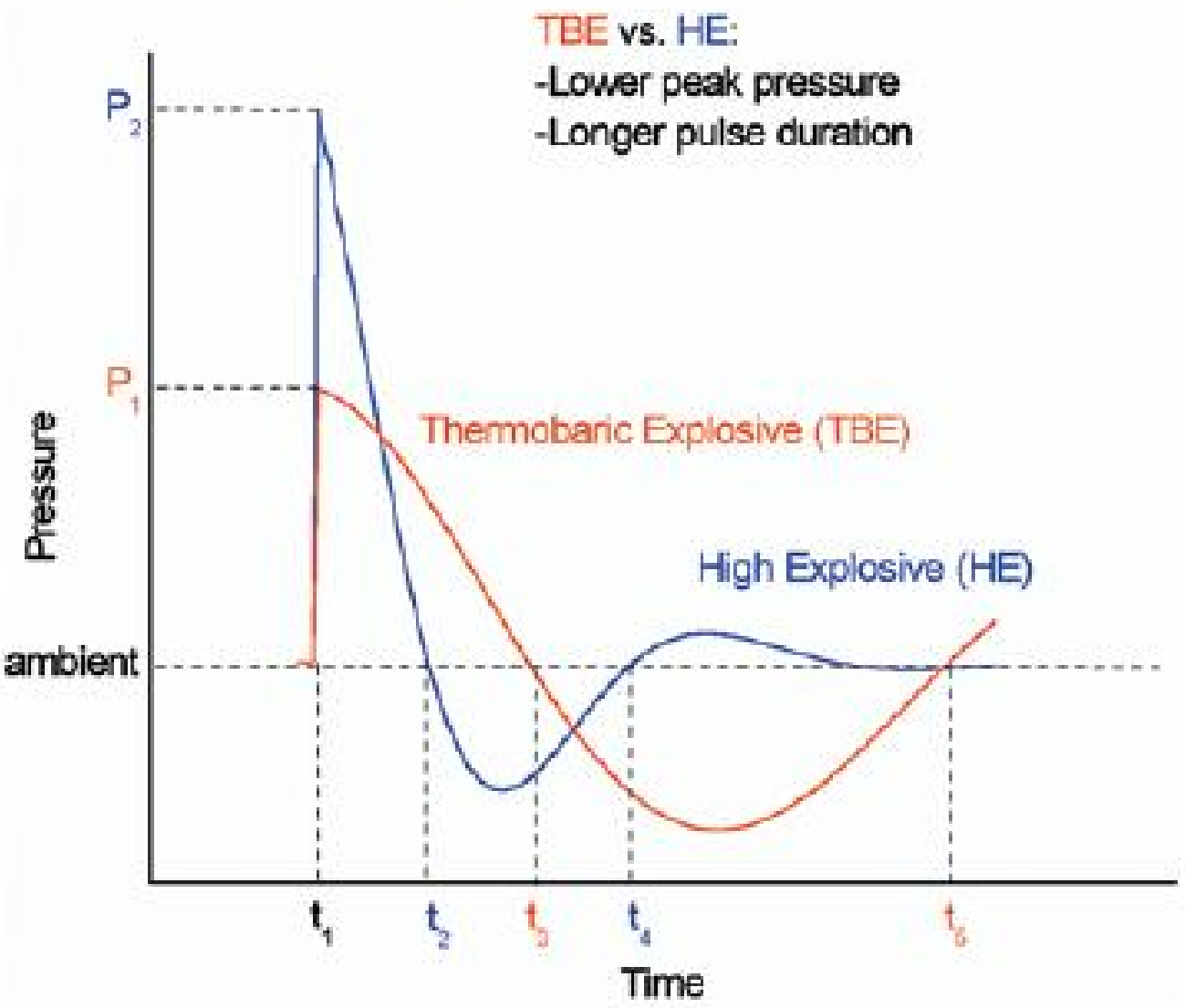
TRAUMATIC BRAIN INJURY PATHOPHYSIOLOGY (BLAST INJURY)

Types of traumatic injury in Blast Injury:

1. Primary blast injury from blast wave itself: complex waves
2. Secondary from flying debris
3. Tertiary caused by acceleration of the body by blast wind: includes impact of body with other objects, coup-contrecoup brain injury
4. Quarternary caused by flash burn and chemical/smoke exposure.

Cernak I, 2010. J Cereb Bl Flow Metab;30:255-266.

1: Pressure history of high explosive (HE) and thermobaric explosive (TBE) detonations

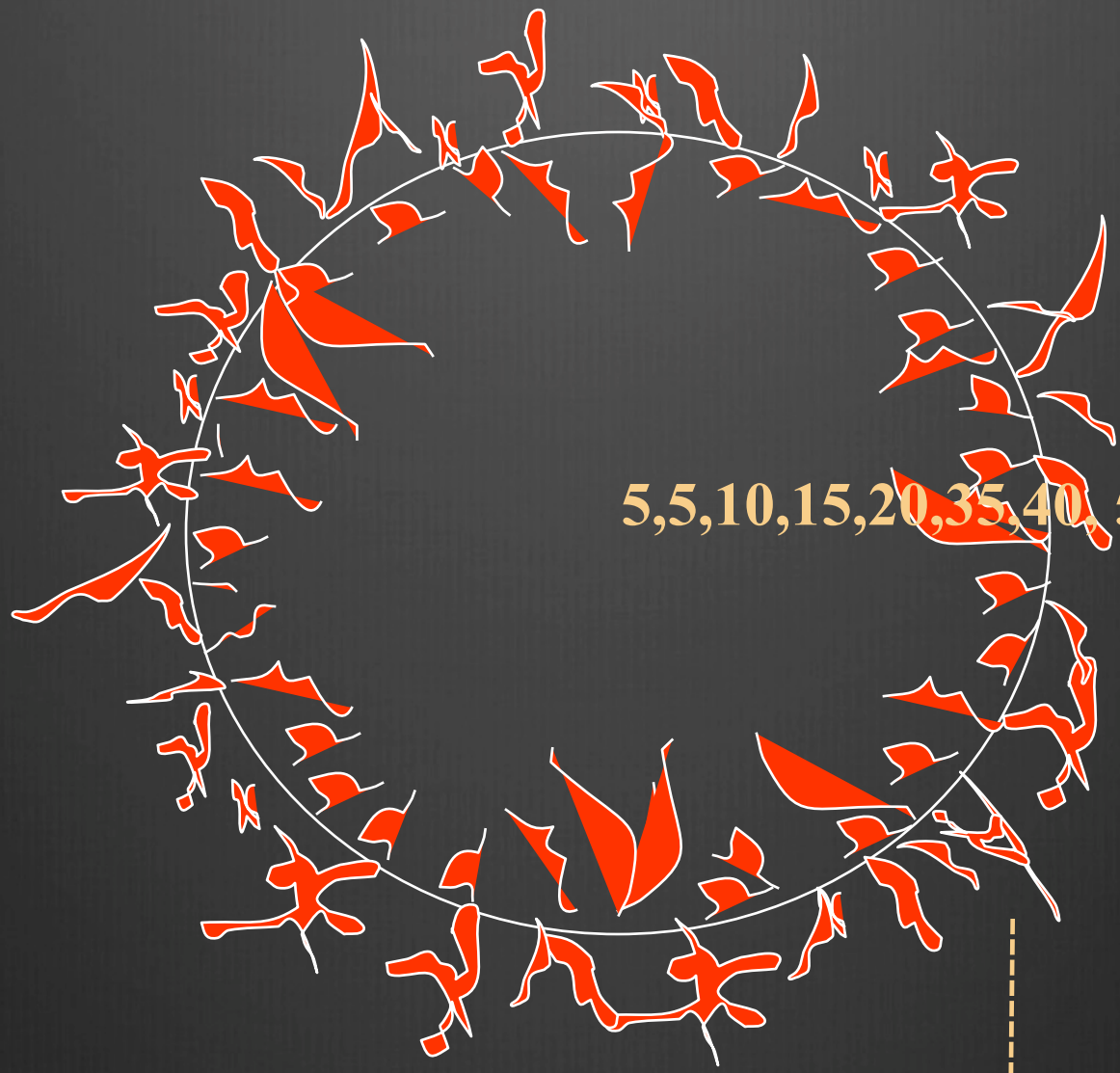


http://www.defence.gov.au/health/infocentre/journals/ADFHJ_apr03/images/adf_wildegger_fm-1.jpg

The net result of traumatic brain injury

Microscopic wounds in gray and white matter consisting of living, dead, and living non-functional brain tissue (Presumption)

Think of the Marx Model



TBI and Neuroinflammation

A plethora of literature has established that neuroinflammation is one of, if not, the dominant pathophysiology in the secondary injury phase of TBI

TBI and Neuroinflammation

Cell Mol Neurobiol (2017) 37:571–585
DOI 10.1007/s10571-016-0400-1

REVIEW PAPER

Pathophysiology Associated with Traumatic Brain Injury: Current Treatments and Potential Novel Therapeutics

Matthew L. Pearn[1,2] · Ingrid R. Niesman[3,4] · Junji Egawa[1,2] · Atsushi Sawada[1,2] · Angels Almenar-Queralt[3,4] · Sameer B. Shah[5] · Josh L. Duckworth[6] · Brian P. Head[1,2]

"TBI results in BBB damage and leakage which allows for… increased neuroinflammation."

"Injury to microglia causes release of cytokines…..igniting an inflammatory cascade at the site of injury."

TBI and Neuroinflammation

Cell Mol Neurobiol (2017) 37:571–585
DOI 10.1007/s10571-016-0400-1

CrossMark

REVIEW PAPER

Pathophysiology Associated with Traumatic Brain Injury: Current Treatments and Potential Novel Therapeutics

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"Injury to endothelial cells, pericytes, astrocytes (and microglia)… promotes further inflammation for months to years."

"It is the secondary or delayed injury that allows for the opportunity for a therapeutic window to prevent progressive tissue damage and loss of function."

TBI and Neuroinflammation

Journal of Neuroimmunology 332 (2019) 112–125

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review Article

The immunological response to traumatic brain injury

Needham E.J.[a,*], Helmy A.[a], Zanier E.R.[b], Jones J.L.[a], Coles A.J.[a], Menon D.K.[c]

[a] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
[b] Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[c] Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK

Inflammation post TBI involves multiple components of the immune system, including cytokines, neutrophils, astrocytes, microglia, T-Lymphocytes, B-cells, autoantibodies, complement, NK cells, Phagocytes…

"No treatments specifically modulate the underlying pathophysiology"

TBI and Neuroinflammation

Journal of Neuroimmunology 332 (2019) 112–125

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[a] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
[b] Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[c] Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK

"The influence of immunological processes on outcome following TBI… Modulation of these processes offers a tangible mechanism to influence secondary neuronal injury and improve patient outcomes…"
(Potential impact on the 25% of TBI patients who proceed to neurodegeneration as a result of chronic inflammation)

TBI and Neuroinflammation

NIH Public Access
Author Manuscript
J Neuropathol Exp Neurol. Author manuscript; available in PMC 2015 January 01.

Published in final edited form as:
J Neuropathol Exp Neurol. 2014 January ; 73(1): 14–29. doi:10.1097/NEN.0000000000000021.

Progressive Neurodegeneration after Experimental Brain Trauma: Association with Chronic Microglial Activation

David J. Loane, PhD*, Alok Kumar, PhD, Bogdan A. Stoica, MD, Rainier Cabatbat, MSc, and Alan I. Faden, MD
Department of Anesthesiology & Center for Shock, Trauma and Anesthesiology Research (STAR), National Study Center for Trauma and EMS, University of Maryland School of Medicine, Baltimore, Maryland

Mice, controlled cortical impact TBI, longitudinal MRI and histology:
Persistent microglial activation in the cortex at one year with
Progressive lesion expansion, hippocampal neurodegeneration,
and loss of myelin.
Biochemical markers of neuroinflammation and oxidative stress were
significantly elevated.

FDA New Drug and Device Proofing Process

1. In vitro experiments.
2. Small animal studies.
3. Large animal studies.
4. Case reports, case series.
5. European and international clinical trials.
6. U.S. clinical trials.
7. CURES Act has changed this process.

Outline

1. FDA drug and device proofing/approval process (old standard)
2. Brief review of TBI
3. Historical review of author's experience with HBOT in chronic TBI
   A. Louisiana divers.
   B. Louisiana boxers. (CTE).
   C. Case series.
   D. Animal study of chronic severe and mTBI.
   E. Pro bono U.S. war veterans (continues to this day).
   F. Review of the literature of HBOT in mTBI/PPCS
4. Satisfying the FDA recommendation of 2011.
5. Conclusion and recommendation for government and insurance reimbursement. Class A, American Heart Level 1.

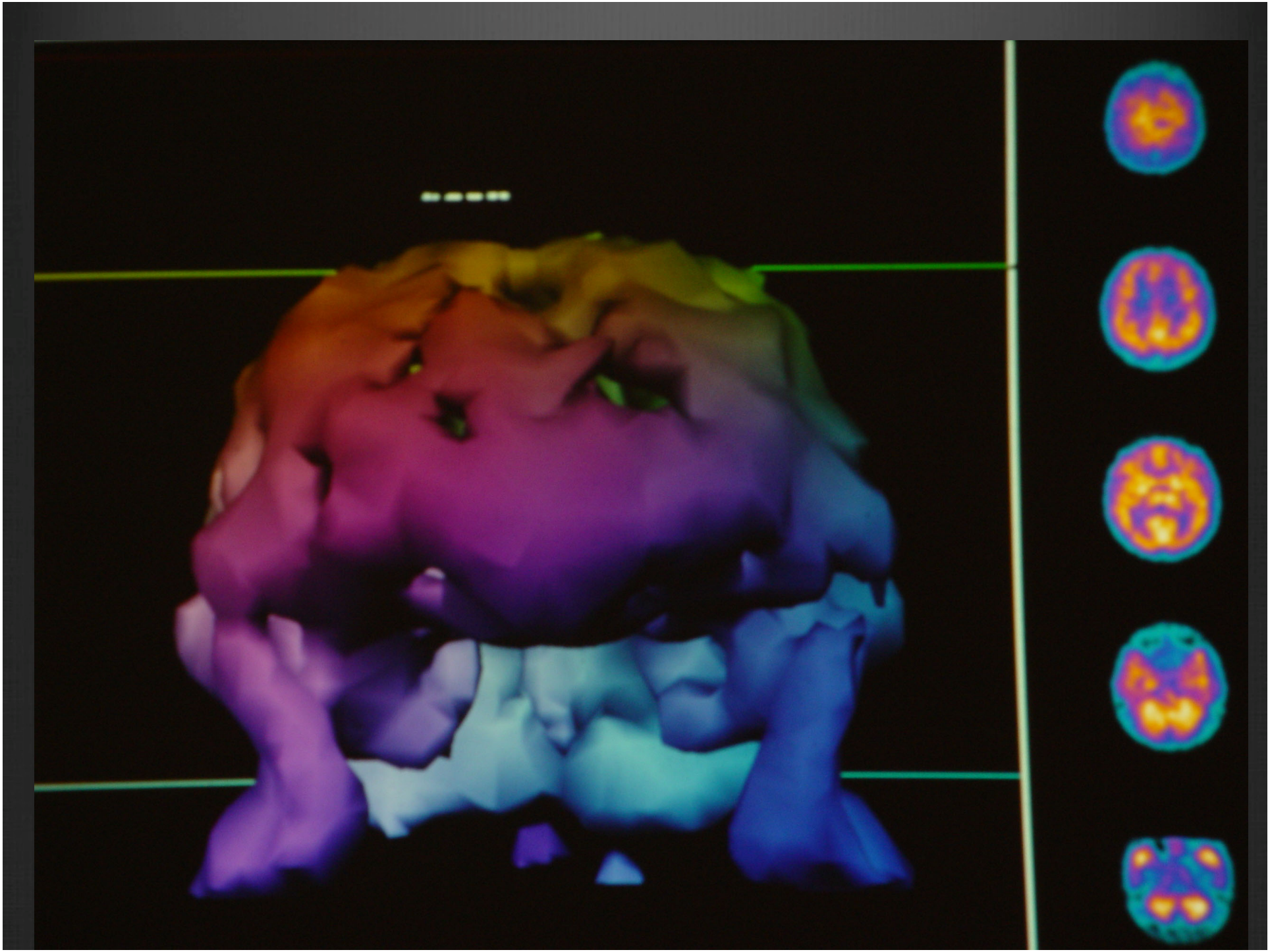
Case Presentation

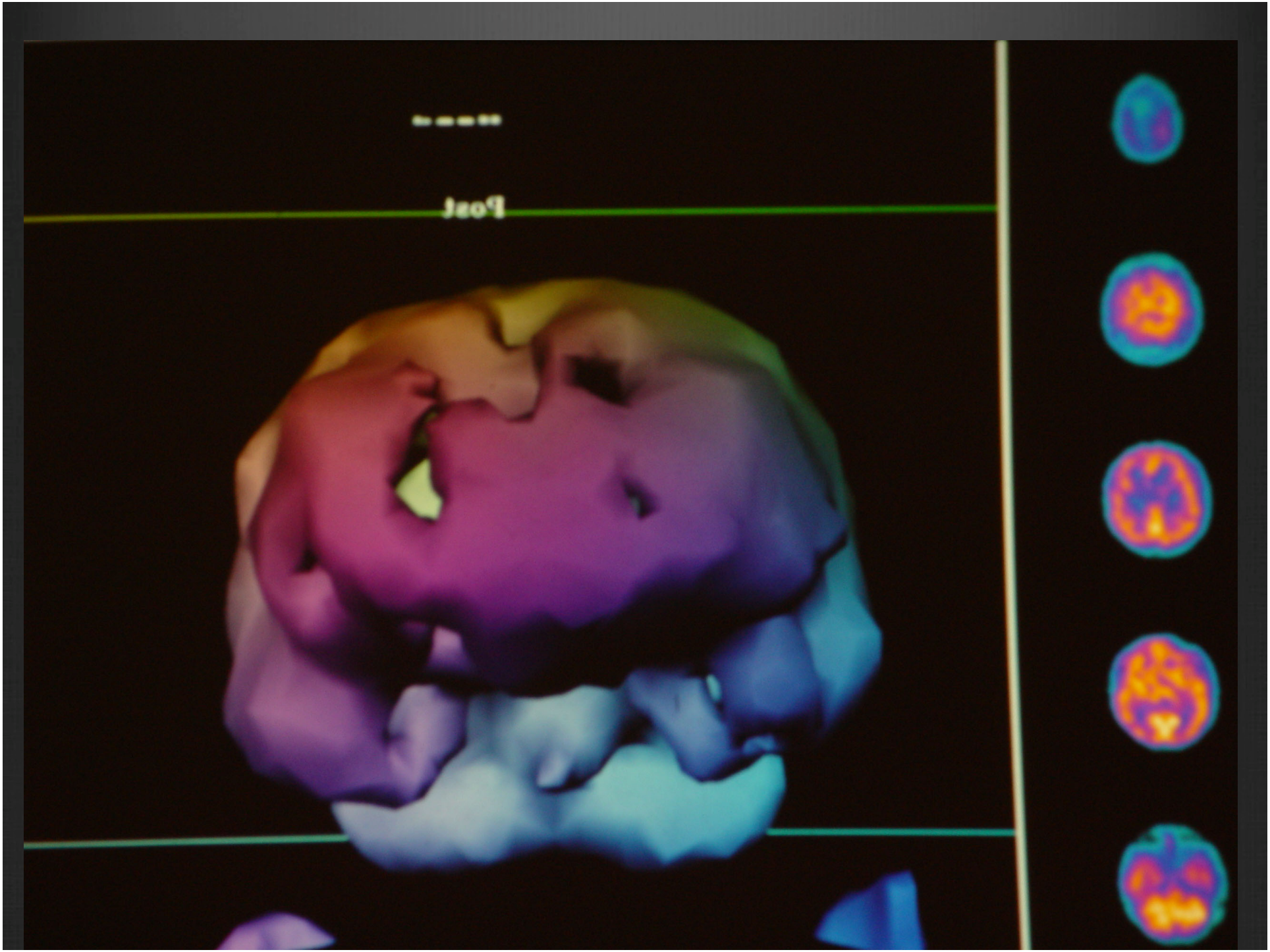
D. G.

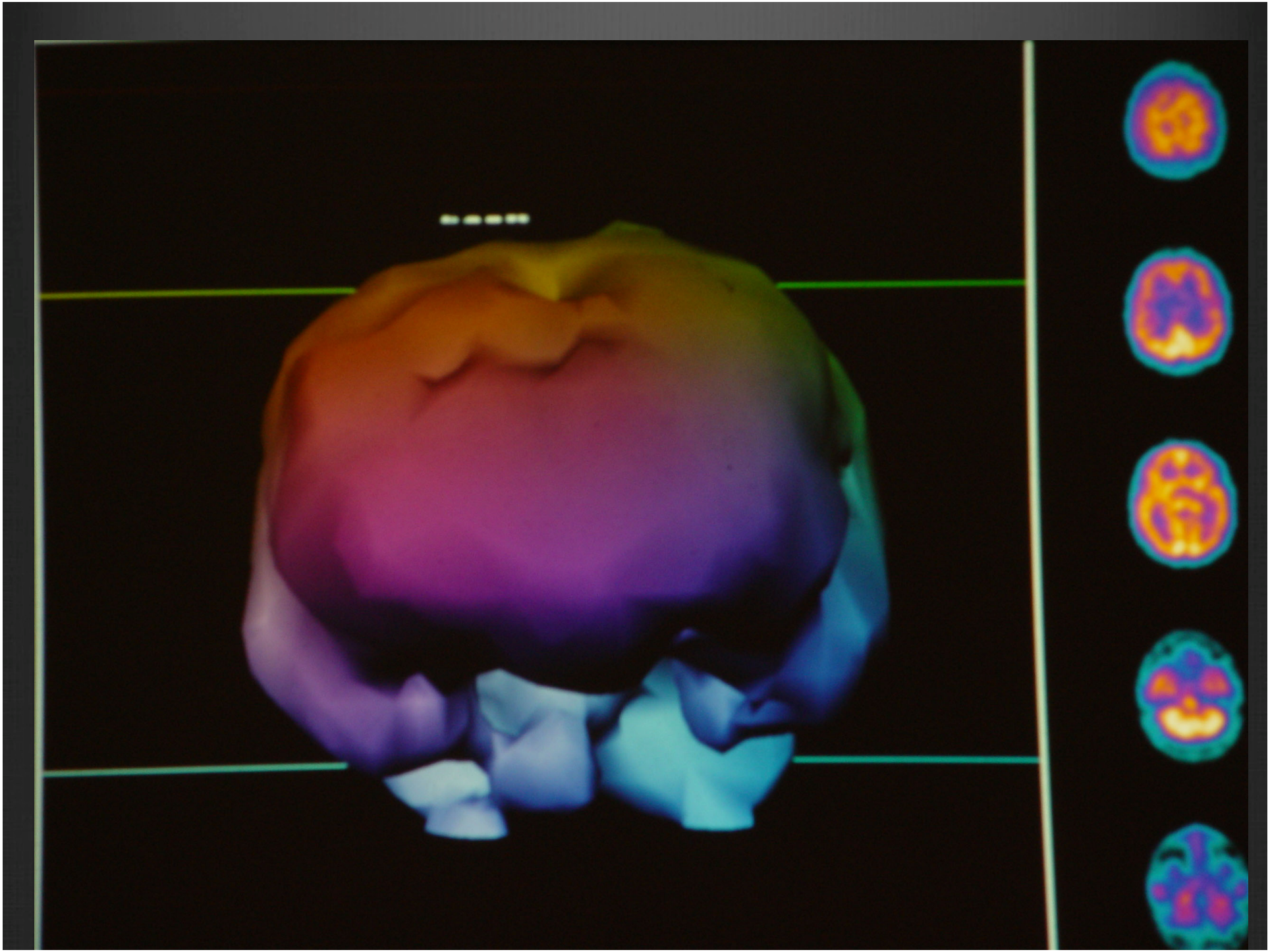
34 y.o. WM Sport SCUBA Diver

Neurological Decompression Illness

5/19/1991







HBOT IN CHRONIC BRAIN INJURY

Early case experience

(New Orleans and Slidell, LA)

1. Gratuitous neurological improvement in extremity wound patients with chronic neurological diagnoses.
2. Divers with subacute cerebral decompression illness.
3. Louisiana boxers: Dementia Pugulistica Study:
   a. Community Hospital IRB
   b. Funded by The Hirsch Foundation ($20,000) to Keith Van Meter, M.D. and Sheldon Gottlieb, Ph.D. of the Baromedical Research Foundation of New Orleans.
   c. I evaluated 3 Boxers, treated two (one was the first case of CTE-1989).

HBOT IN CTE

Dementia Pugulistica Study

Case Presentation

R.D.

55 y.o. male

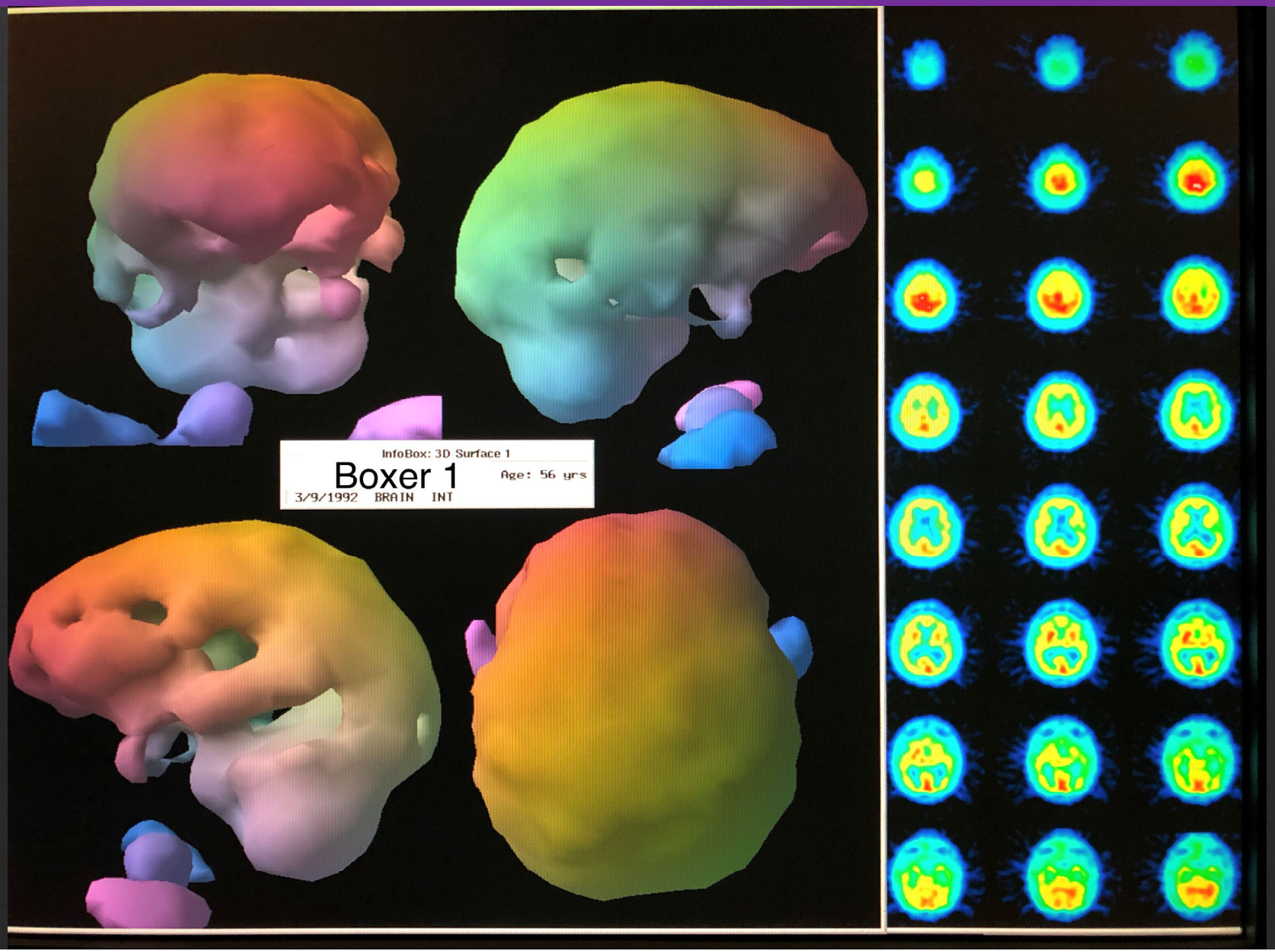
Boxing 15-32 y.o., 15 years professionally

135 professional bouts, last one 23 years before HBOT

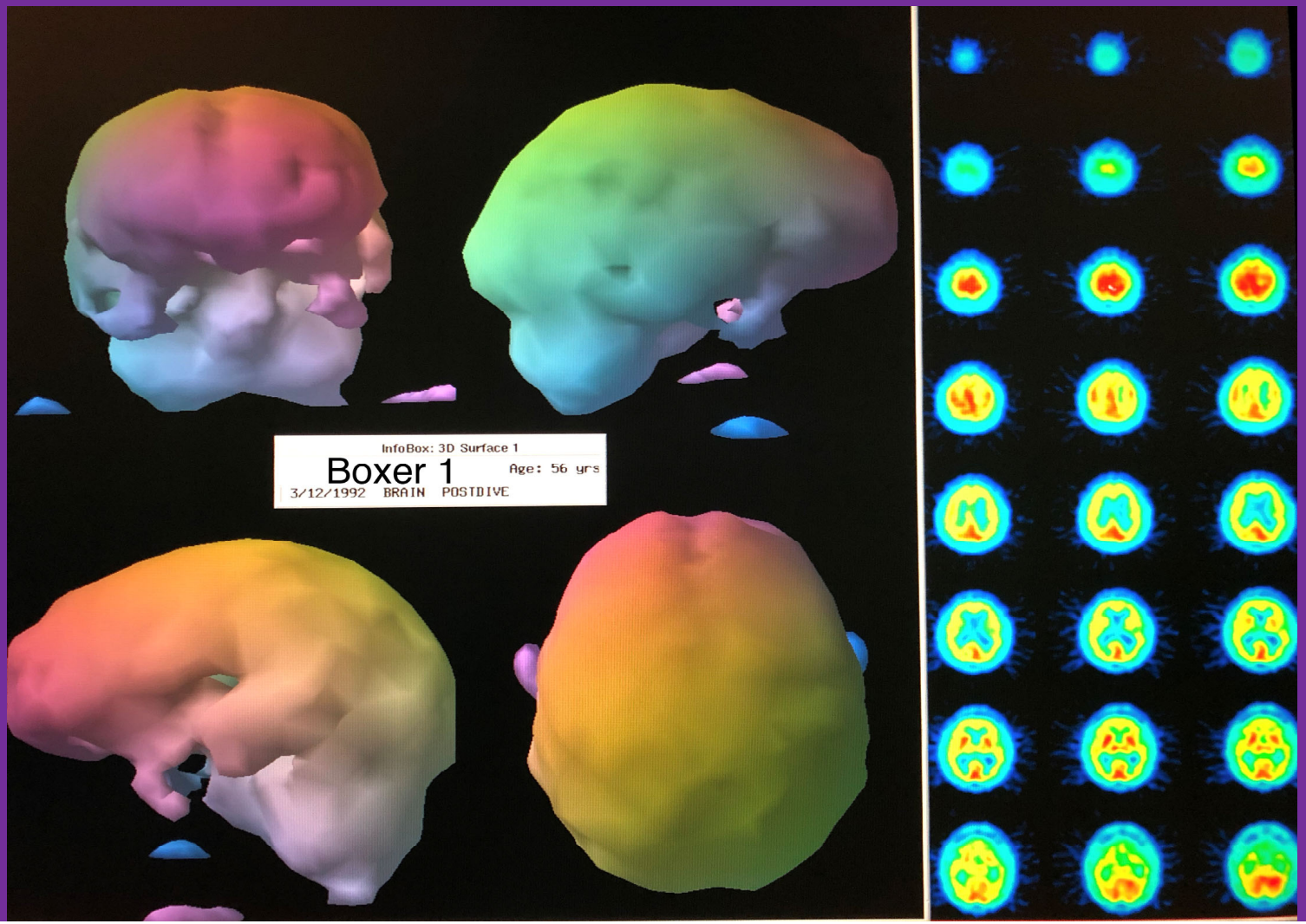
World champion

1 LOC in 1st 100 bouts, 4 LOCs in last 5 fights, last LOC x 3-5 mins.

SPECT: 5d post 62nd HBOT-Surface Reconstruction 3-D



SPECT: after 63rd HBOT-Surface Reconstruction 3-D after single HBOT at 2.0 ATA/70 Minutes



Hyperbaric Oxygen Therapy in Chronic Severe TBI

B. N.

29 y.o. WF

6 years after

self-inflicted GSW

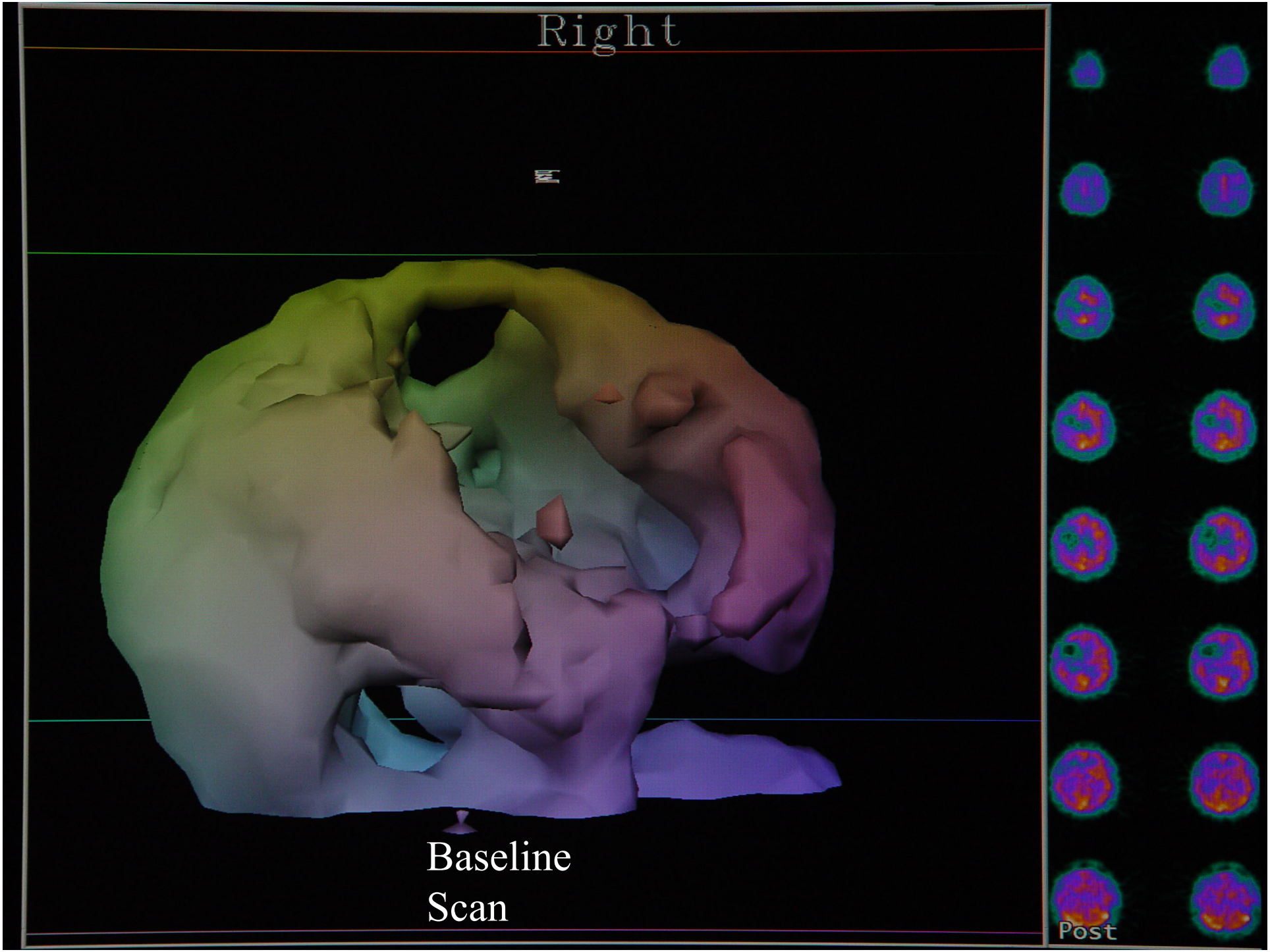
in 1989

B. N.

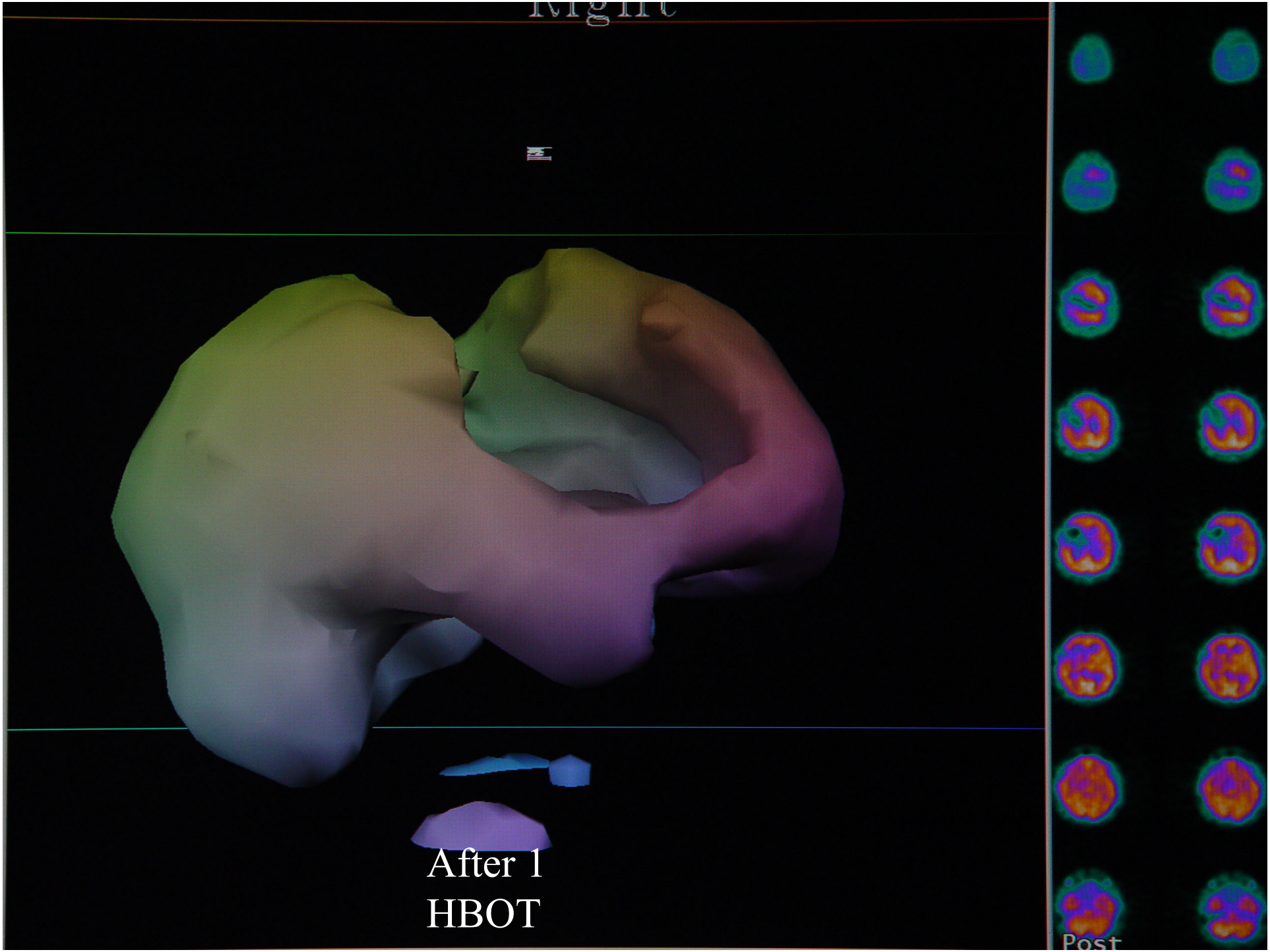
- GSW 1989, coma, prolonged recovery.
- Evaluation in N.O. 6 years later, 1995.
- Paraparetic, severe weakness arms/hands, severe spasticity, spasms with inability to sleep, headaches, poor trunk control, severe constipation.
- SPECT and HBOT over 4 months.

B. N.

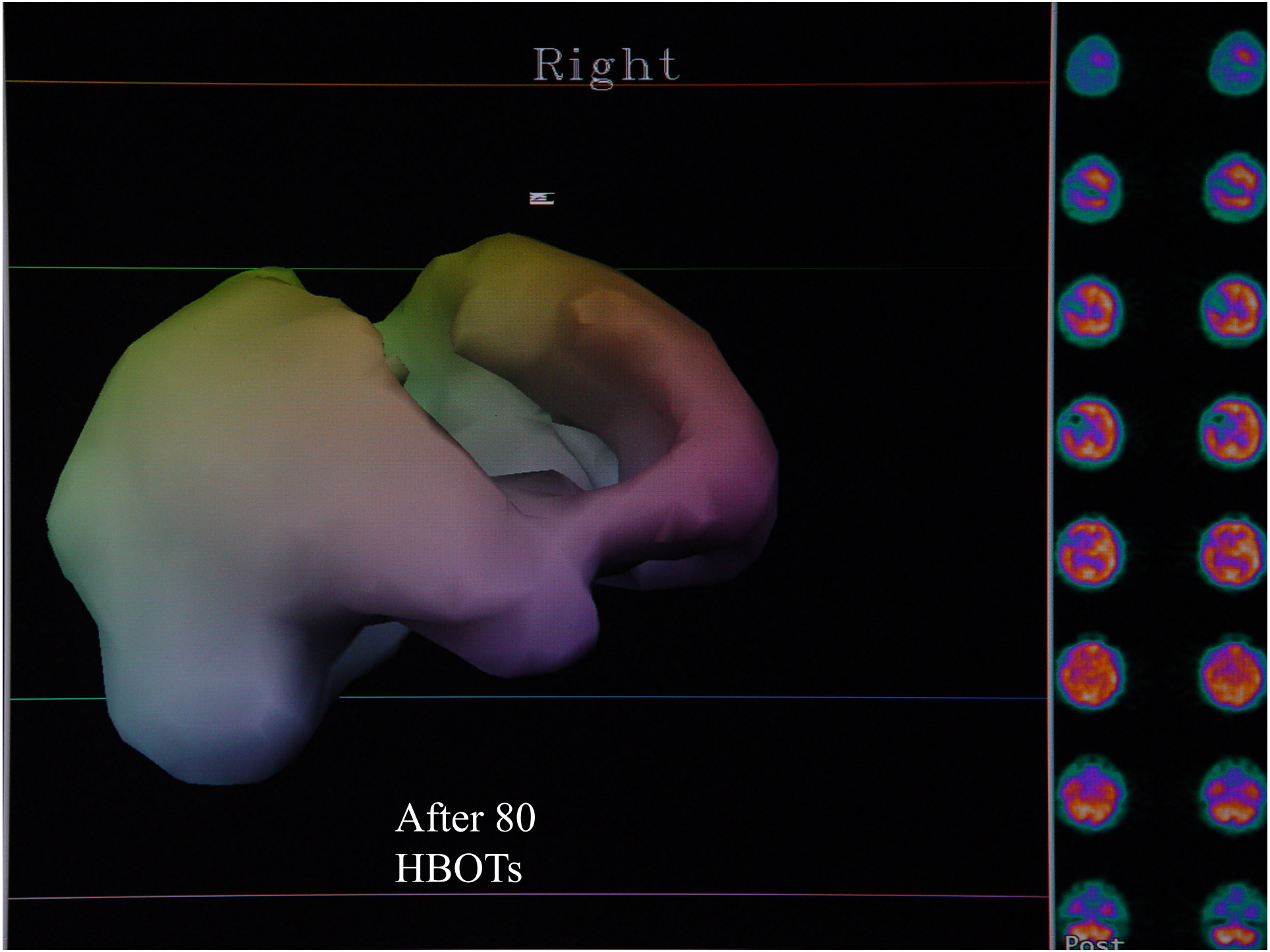
- Results: Independent physiatrist evaluation—generalized decrease in spasticity, increase left hand grip, movement in knees.
- Patient reports: increased extremity and trunk motor function, decreased headaches, marked decrease in night spasms with reduction of insomnia, natural bowel movements.
- SPECT: fairly dramatic improvement in brain blood flow.



Baseline
Scan



After 1
HBOT


Right
After 80
HBOTs
Post

What's the difference between chronic extremity and chronic brain wounds?

Location, and potential responsiveness to a different dose of HBOT

Perfusion/Metabolism Encephalopathies Study

Results:

~ 200 patients evaluated

~ 50 different neurological conditions especially CP, DCI, TBI, CVA, CO, near-drowning, autism, toxic brain injury

HISTORICAL REVIEW OF HBOT IN mTBI/PPCS: Origin of the 1.5 ATA Dose

1. Noticed response of divers with greater and greater delay to treatment using a lower dose of HBOT (1.5 ATA) per Dr. Richard A. Neubauer. It was the dose used by German neurosurgeons in the 70s for acute severe TBI and the same dose that I found was effective for acute concussion the first NFL player I treated with numerous acute concussions in 2001 (Bill Romanowski), numerous family members in the mid-2000s, my wife in 2008, a Colorado hyperbaric clinic in dozens of acute concussed skiers in the 2000s and thru to the present, North Carolina physicians for acute concussion in the late 2000s, and of late in multiple places in the U.S.

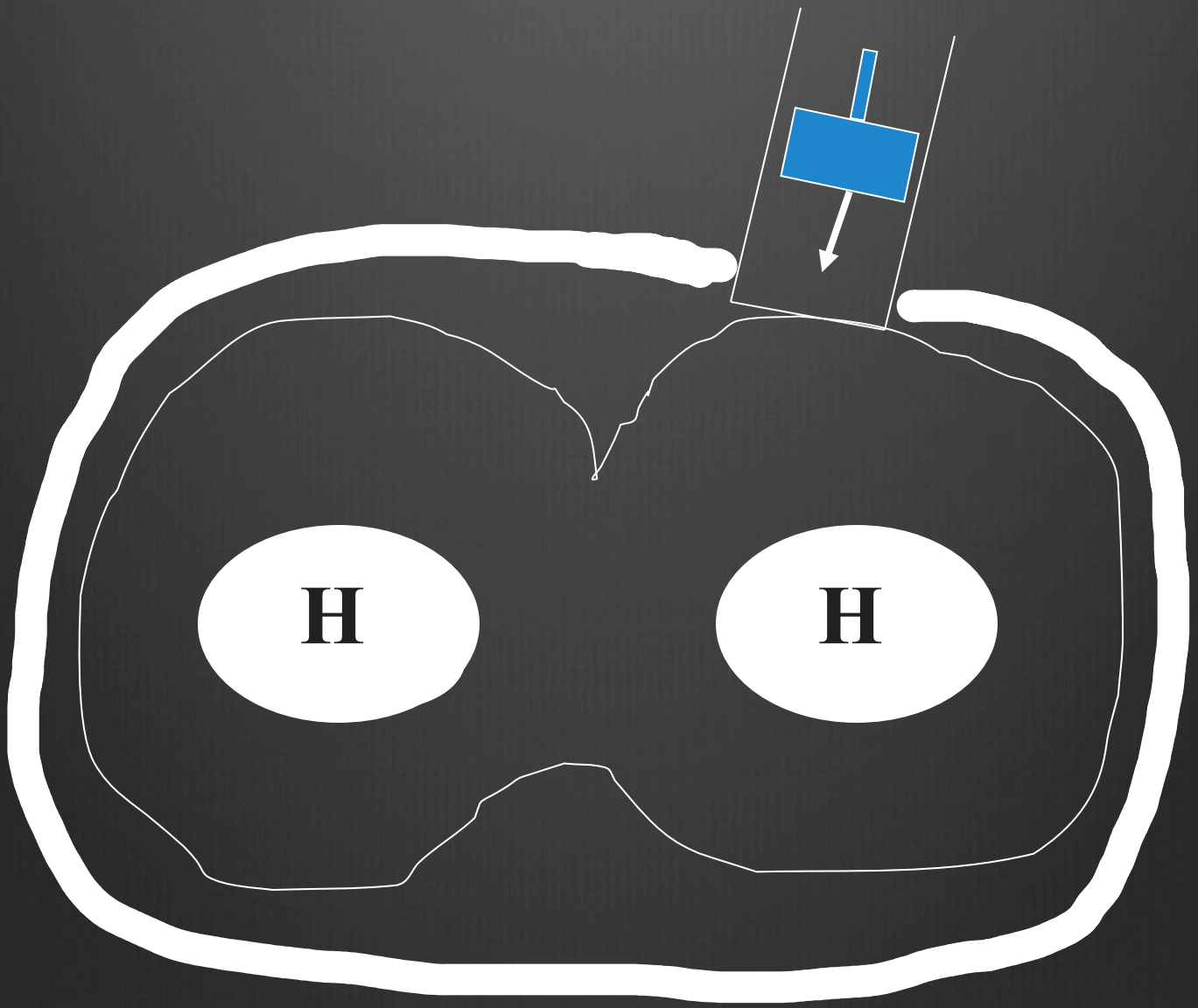
“But, You Don’t Have an Animal Model”

UHMS Annual Meeting 1994, Denver

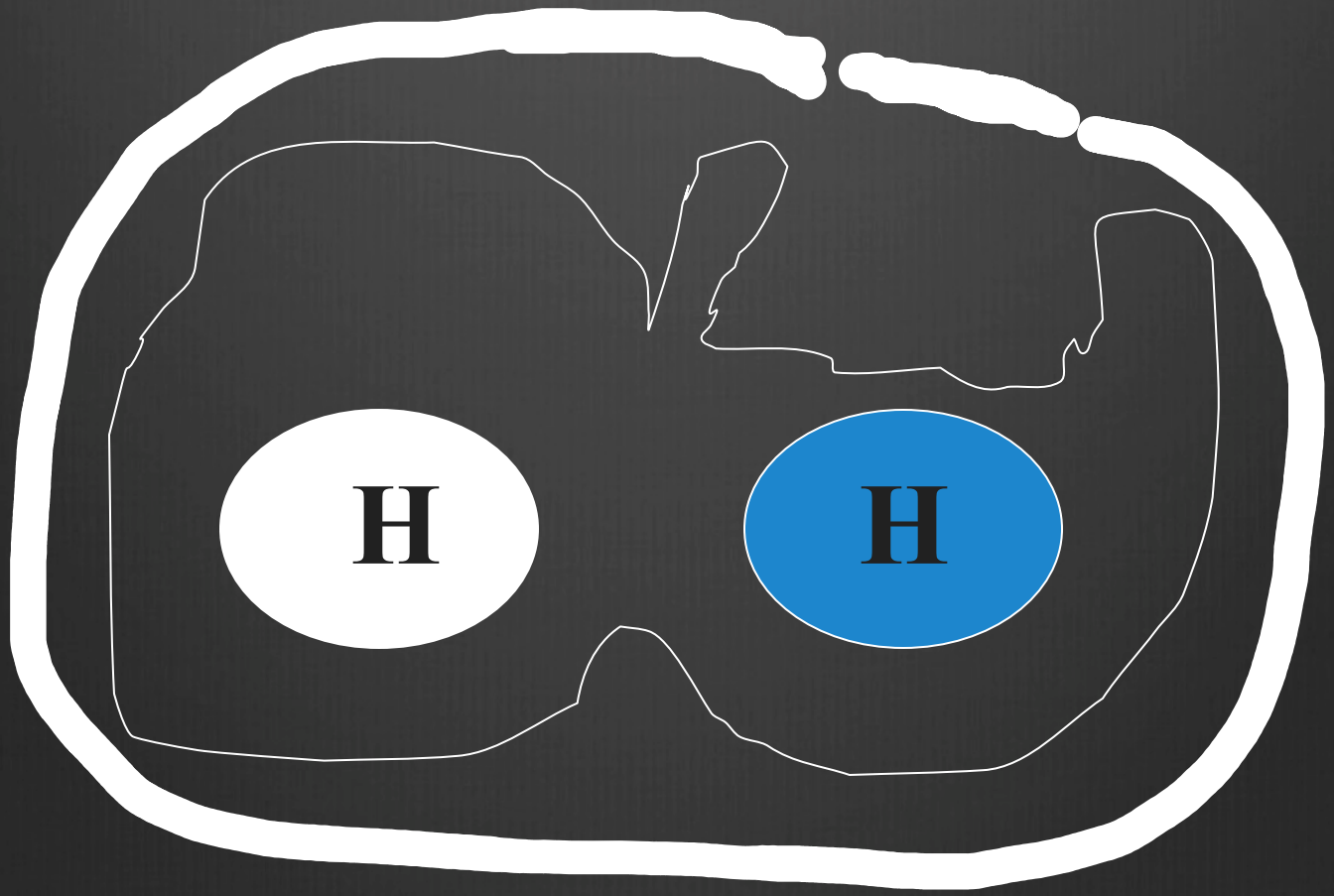
Focal Cortical Weight Drop (Head Bonk) Model of Acute Traumatic Brain Injury

Adapted to Chronic Brain Injury

Head-Bonk Before



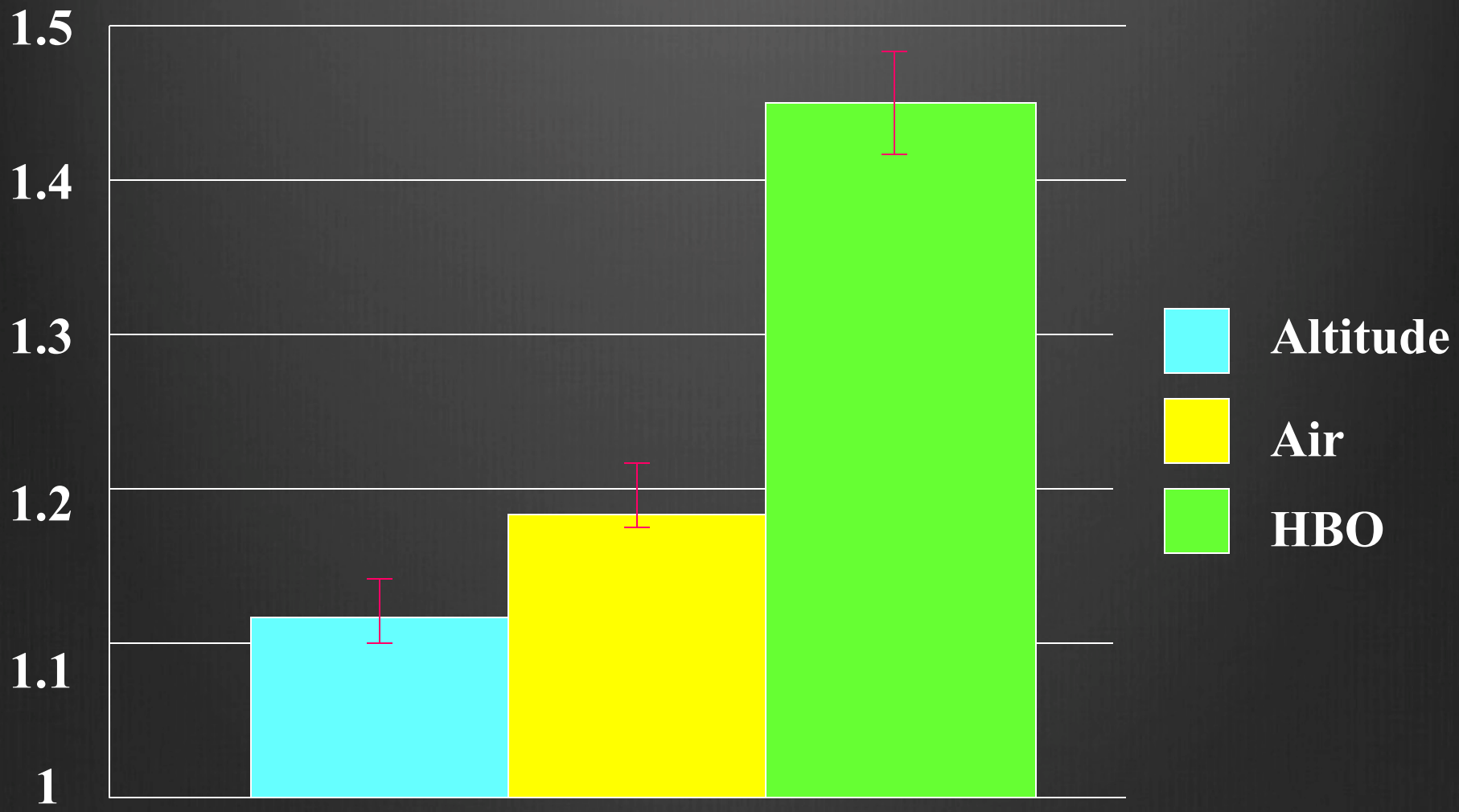
Head-Bonk - 30 D After

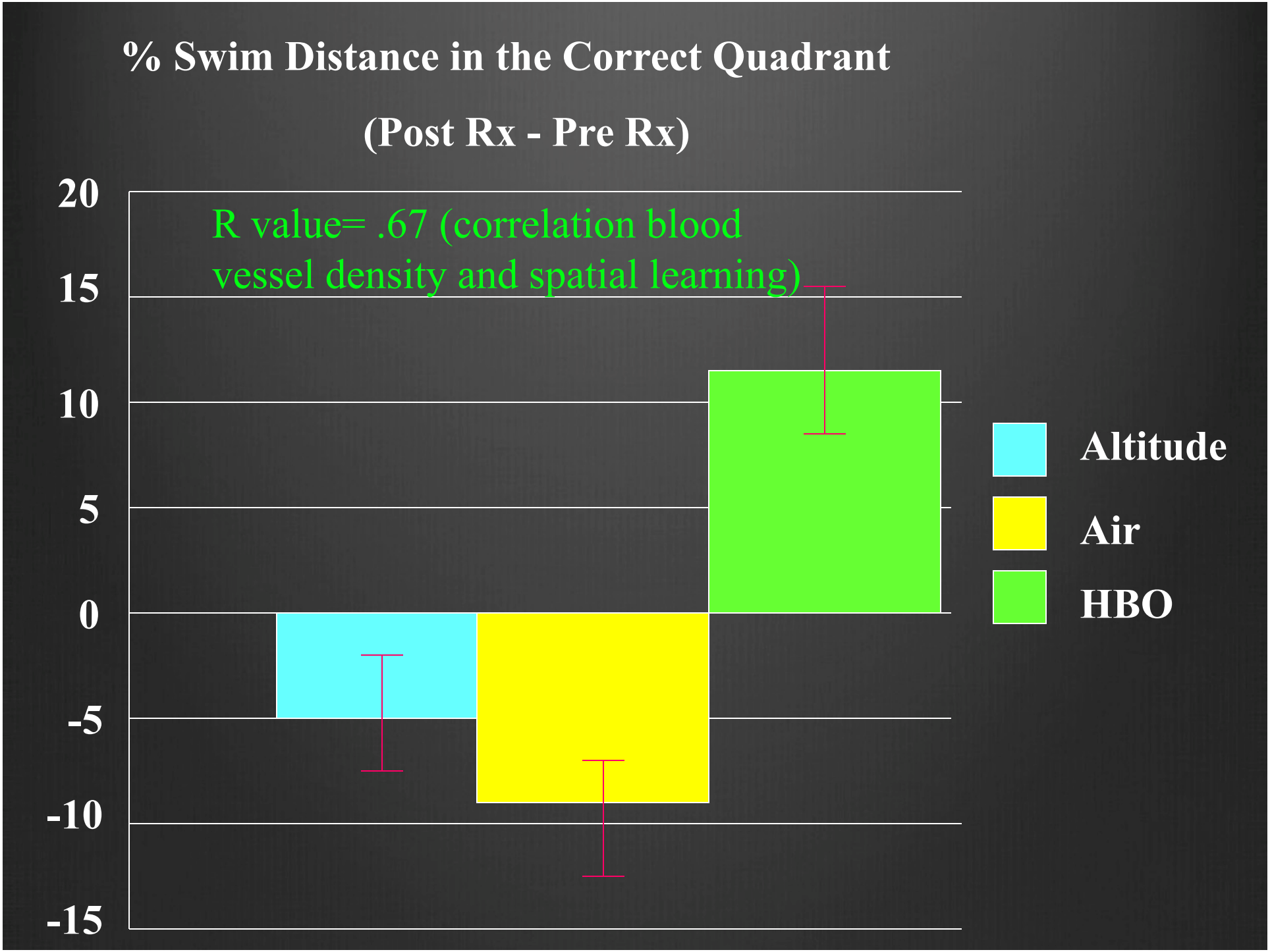


Head-Bonk -Protocol

- Bonk
- 30 d later Morris Water Task
- Ship rats to New Orleans from Albuquerque to New Orleans. One group remains in Albuquerque as an altitude control (5,595 ft).
- 50d post injury: randomly assign to HBOT 1.5 AT A/90 mins., bid, 7d/wk. x 80 or HBA (1.1-2 ATA x 5-10 mins. and drift back to 1 ATA in 15 minutes/90 mins., bid, 7d/wk.
- Ship to Albuquerque
- Morris Water Task 10 days later then sacrifice all groups and stain with peroxidase stain for red blood cells. Measure blood vessel density and spatial learning and memory.

Vessel Ratio, Ipsi:Contralateral Hippocampus




% Swim Distance in the Correct Quadrant
(Post Rx - Pre Rx)
20
15
10
5
0
-5
-10
-15
R value= .67 (correlation blood vessel density and spatial learning)
Altitude
Air
HBO

Significance of Head Bonk Experiment:

Consistent with & Reinforced:

1. Clinical effects of HBOT in Chronic Brain Injury Patients
2. SPECT changes in HBOT/Chronic Brain Injury Patients
3. SPM/HBOT/SPECT data in Pediatric Brain Injury (medial temporal lobe/clinical findings)
4. To date: only improvement in animal chronic brain injury in the history of science.

Mild TBI Persistent Post-Concussion Syndrome, PTSD, and Hyperbaric Oxygen Therapy

Review of the Clinical Literature

HBOT in Blast-Induced TBI

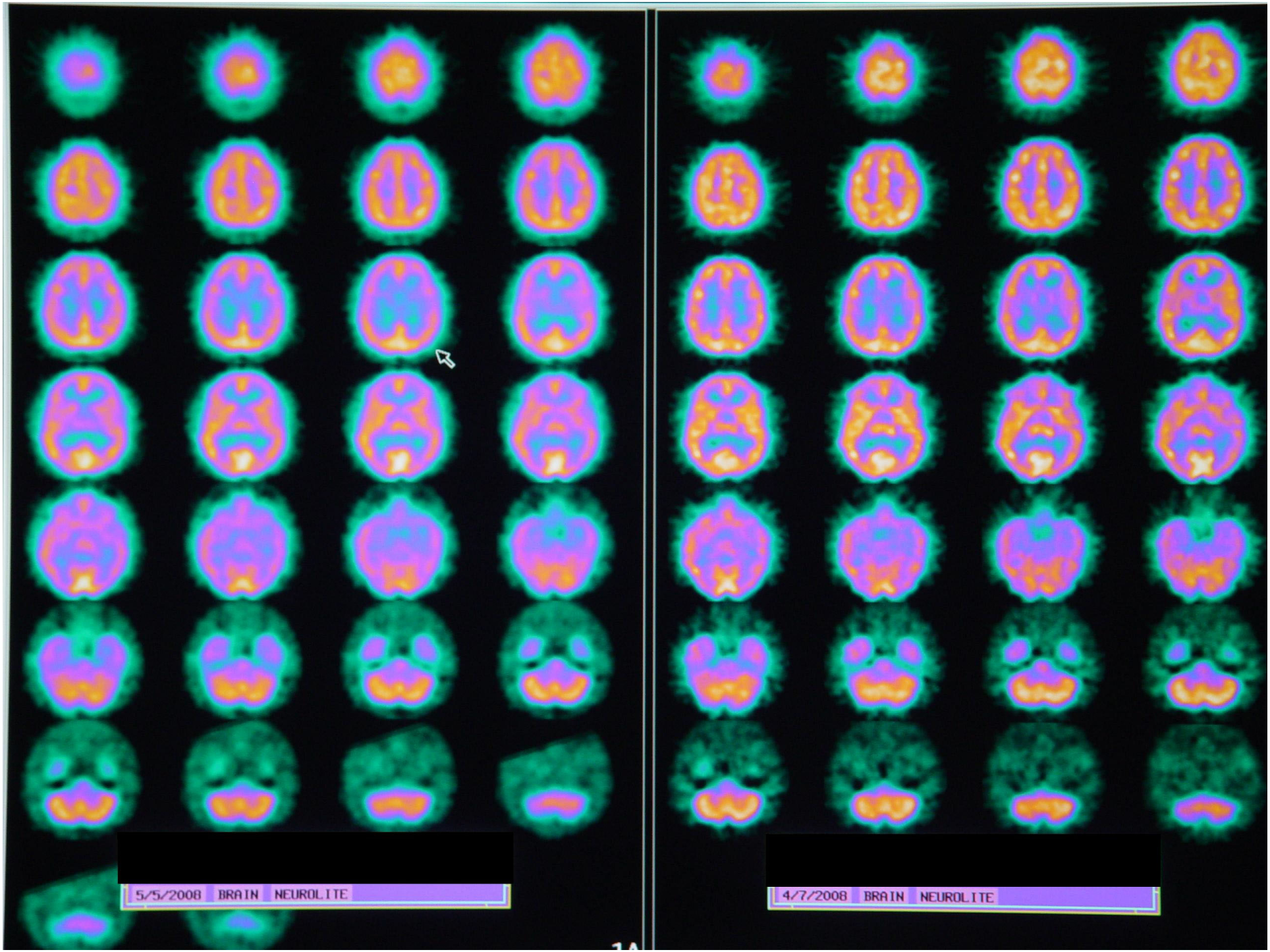
- Case Presentation: General Maney
- 8/21/05: IED explosion with transient LOC, few second anterograde memory loss.
- Walter Reed: extensive evaluation. Cognitive deficits ("low normal" range on psychometric testing).
- PT, aqua-therapy, cognitive therapy (beneficial), but still significantly impaired/unemployable.
- HBOT: 1 year post TBI. Dr. Zant gives wife Harch Protocol (1.5 ATA, 40 HBOTs; optional break, repeat 40 HBOTs)
- Noticeable improvement at 18 HBOT's.
- 25 HBOT's: much more sociable, less napping.
- 80 HBOT's: significant improvement in cognition and reduction in back pain,.
- Returns to part-time work as judge.

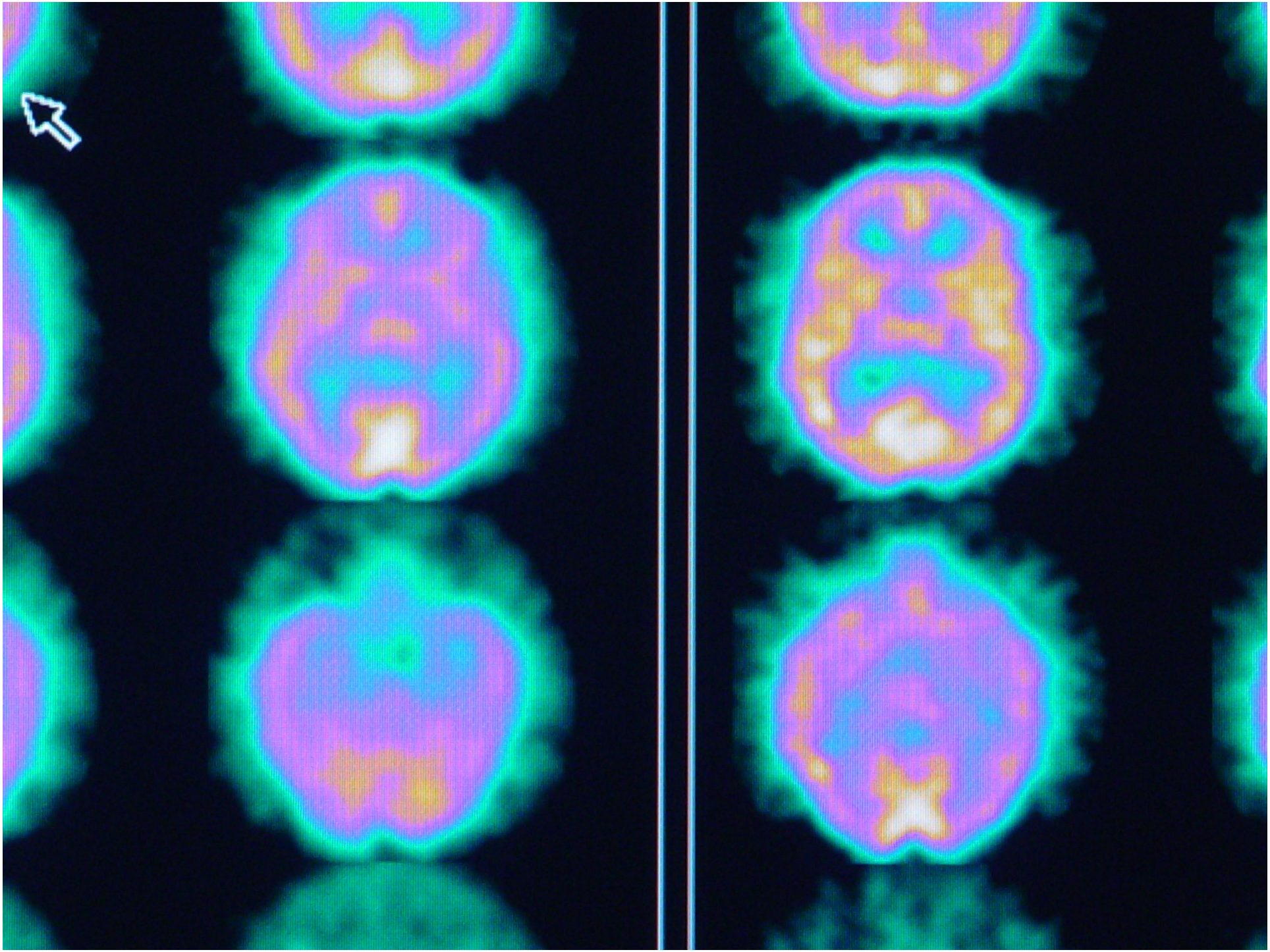
HBOT in Blast-Induced TBI-2nd Case Cases Journal, 6/2009

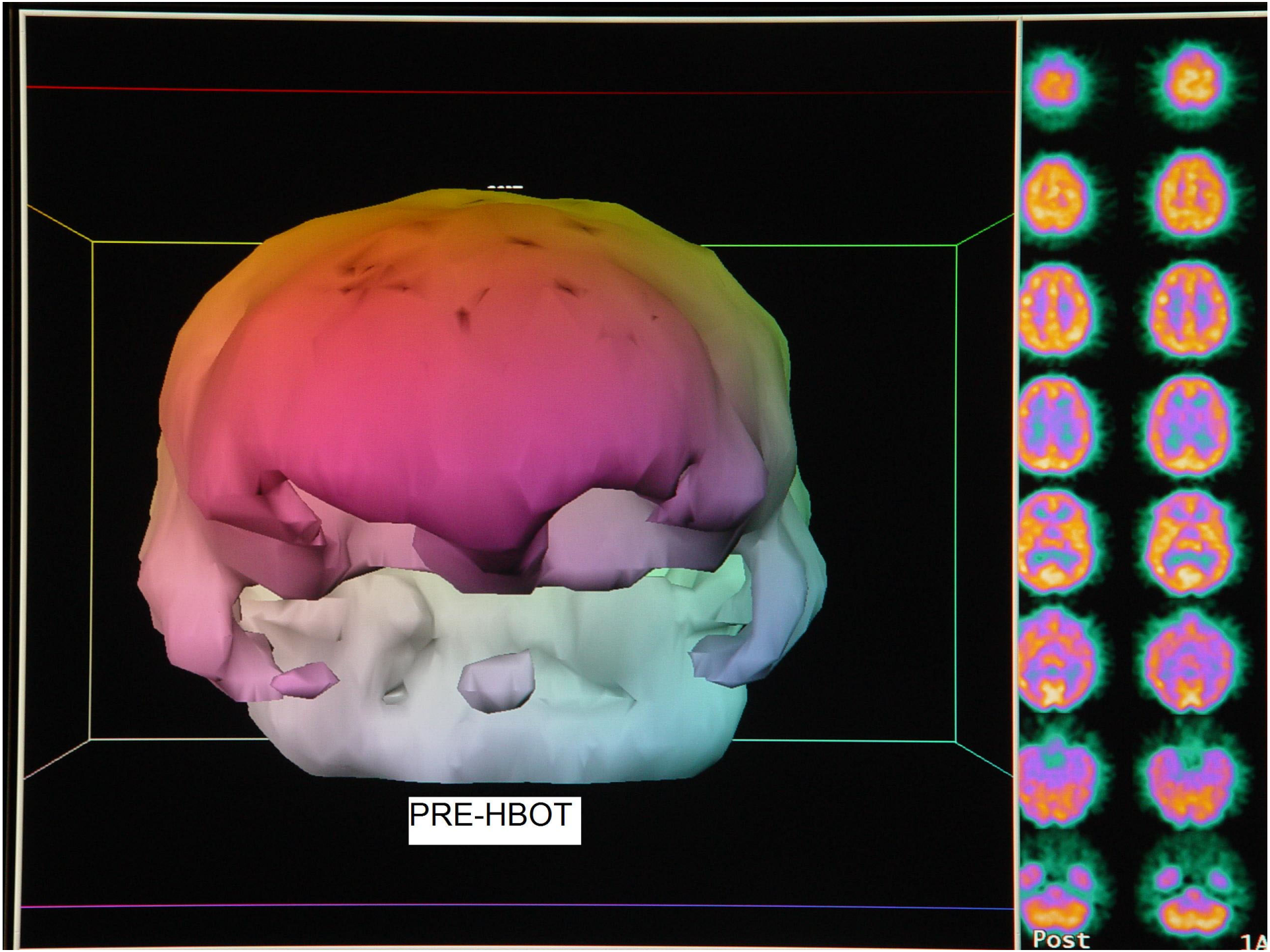
- Boston judge responds to USA Today PGH offer.
- 25 y.o. Marine machine-gunner (Humvee).
- IED explosion 3/15/05 w/LOC <1min.
- Tinnitus, headaches, off-balance, irritability.
- 6 more IEDs and RPGs with altered LOC in this and 2nd deployment.
- Bilateral tinnitus, hearing loss, nightmares, behavioral and cognitive deterioration.
- Honorable D/C with 10% PTSD, 10% TBI

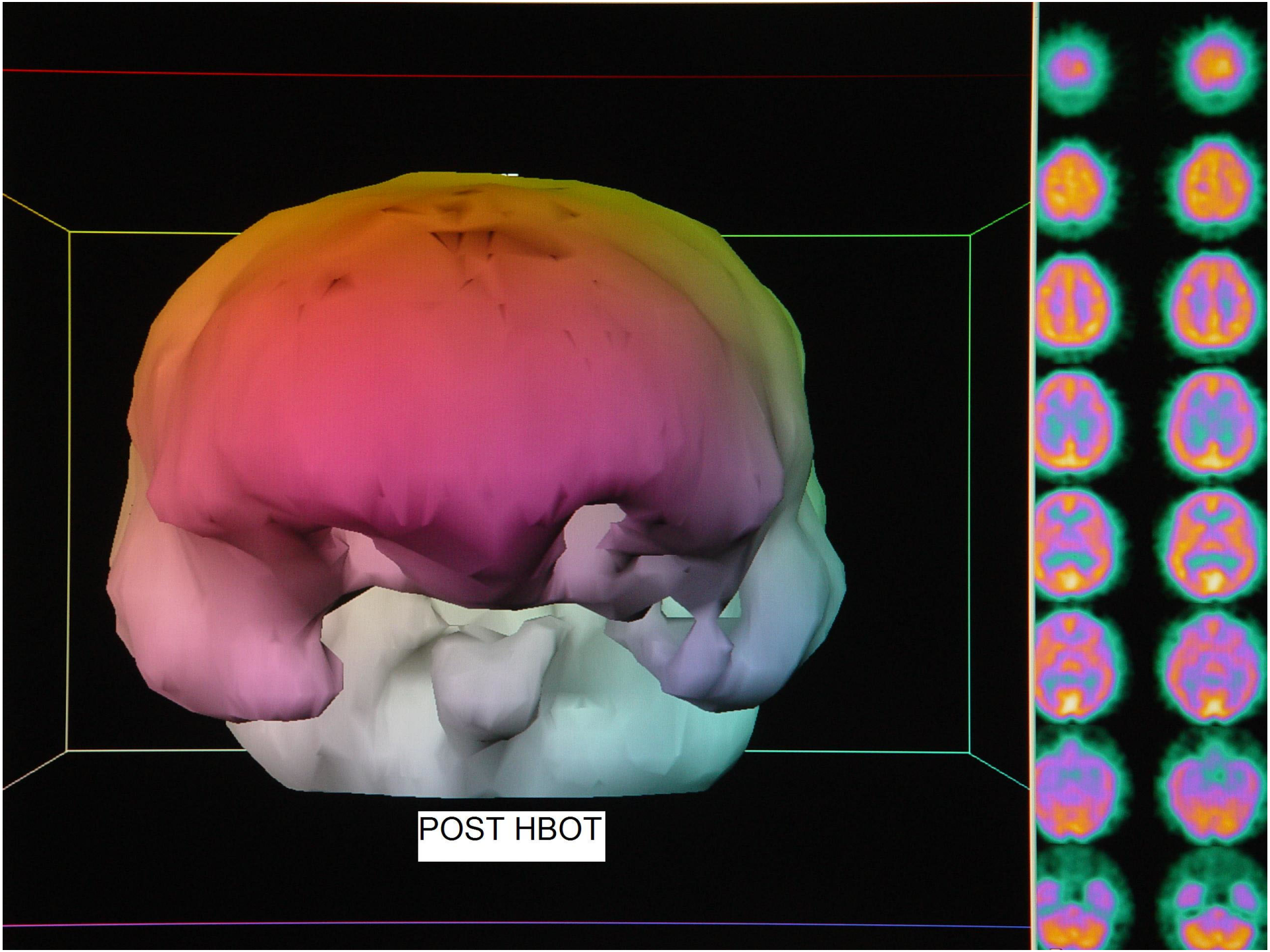
Harch, et al. *Cases Journal*. 2009;2:6538.

- 4/7/08: 3y post injury. H & P, SPECT brain imaging.
- (39 HBOTs, 4/7-5/2/08).
- 1st HBOT: HA's gone
- 8th HBOT: Sleeping all night-1st x in 3 yrs.
- 12th HBOT: Energy up. Tolerates crowds. Goes to French Quarter Festival-400k people in 1 day.
- 25th HBOT: PTSD GONE!
- 39th HBOT: Most Sx, PEx, SPECT improved or gone
- Obtains additional 40 HBOTs .
- 5/2014: gets married, obtains Masters Degree, good QoL


5/5/2008 BRAIN NEUROLITE
4/7/2008 BRAIN NEUROLITE




PRE-HBOT
Post


POST HBOT

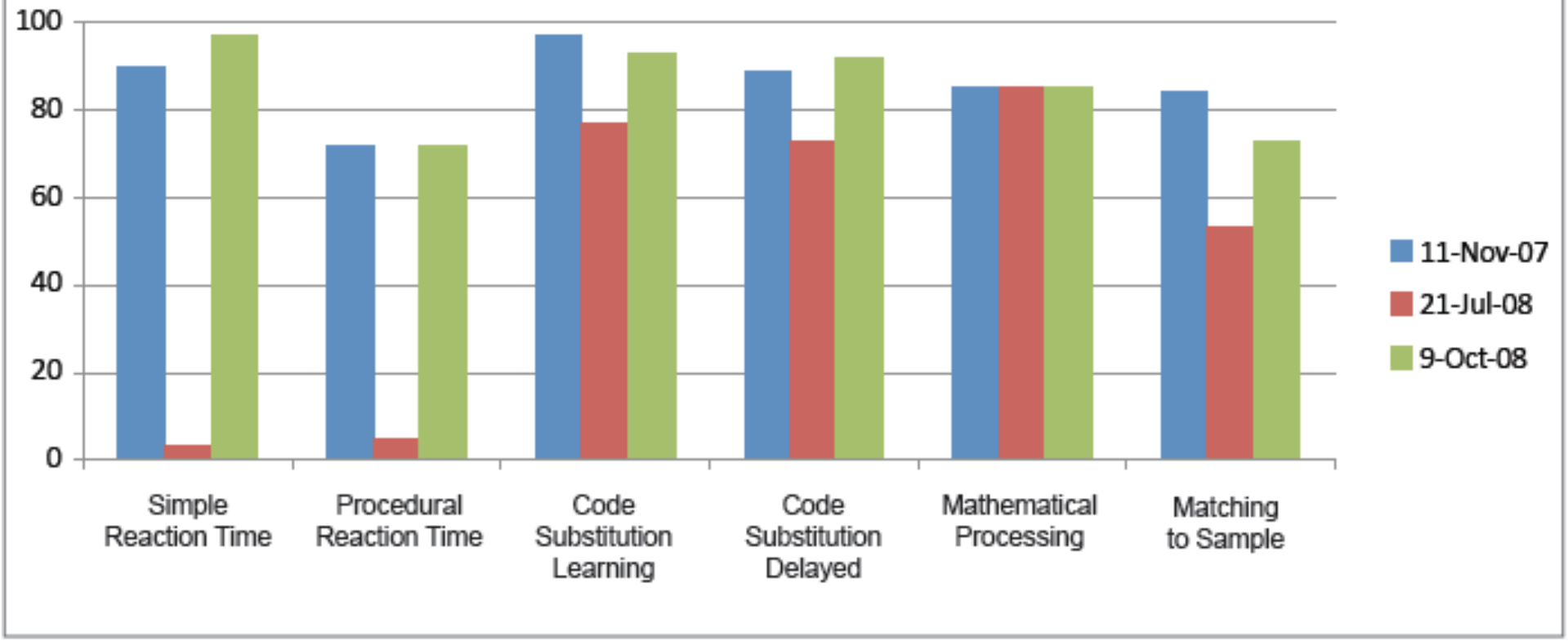
Case Report-Treatment of mTBI with HBOT: Wright, et al, UHM, 2009;36(6)

- 2 U.S. Airmen, IED, acute concussion. Sx for 2 weeks.
- Recurrence of symptoms and additional Sx 3 wks. post injury.
- 6 months post IED, Dx: PPCS. Deterioration of ANAM compared to pre-injury.
- 8 months post IED: HBOT 1.5 ATA/60 qd x 40.
- Repeat ANAMs: return to pre-injury levels. Repeat NP testing showed limited improvement compared to pre-HBOT. One airman returned to full duty. The other was still symptomatic and received another 40 HBOTs. He returned to his pre-injury functional state.

Case Report-Treatment of mTBI with HBOT: Wright, et al, UHM, 2009;36(6)

ANAM Scores

FIGURE 1B — *Airman C ANAM Scores*

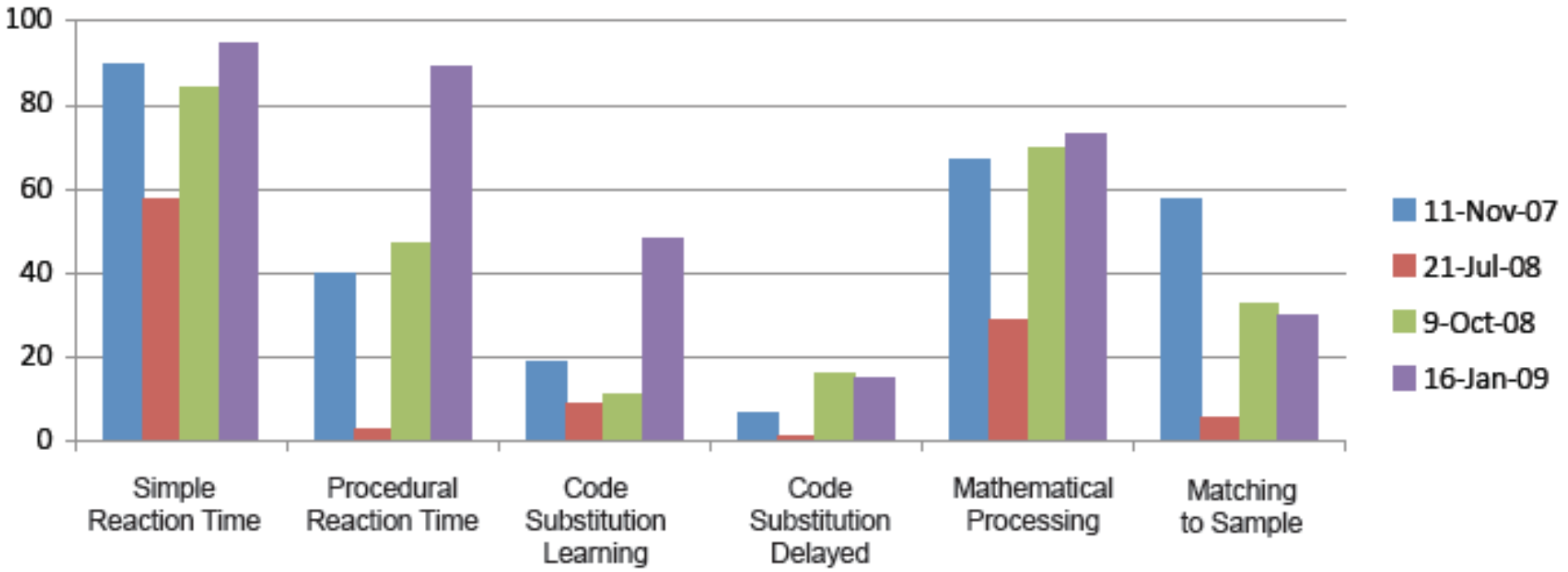


Throughput scores are presented as the percentile of the comparison group of military members without TBI.

Case Report-Treatment of mTBI with HBOT: Wright, et al, UHM, 2009;36(6)

ANAM Scores

FIGURE 1A — *Airman B ANAM Scores*



On 8/14/2008 the first case report and 4 additional cases of blast-induced mild-moderate TBI/post-concussion syndrome treated with were presented to the Navy Surgeon General, Assistant Commandant of the Marine Corps, the ex-Secretary of the Army, wife of chairman JCOS, and an august group of military dignitaries, military medical experts, and congressional staff. In the audience were 3 of the 6 cases who provided their testimonials. The purpose of the presentation was a request for funding. Funding was assured, but never materialized. As a result, we self-funded a pilot trial.

Hyperbaric Oxygen Therapy in Chronic Blast-Induced Mild-Moderate Traumatic Brain Injury (Post-Concussion Syndrome) and Post-Traumatic Stress Disorder (LSU IRB #7051)

LSU School of Medicine, New Orleans and Baromedical Research Institute of New Orleans

September, 2008

$643,000 raised by Bill Duncan, Marty Hoffman, and Dr. Harch.

Harch, PG, et al. A Phase I Study of Low Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post Concussion Syndrome and Post Traumatic Stress Disorder. Journal of Neurotrauma, Epub ahead of print, 11/22/2011: 2012, 29(1):168-185.

LSU Pilot Trial

Study approved 8/2008

HBOT in Chronic TBI and TBI with PTSD-LSU Pilot Trial

- **Protocol: ≥ 1 mild-mod TBIs w/LOC, > 1 yr old**
  - **Screening/History/Physical Exam/Full NP battery, SPECT, QoL questionnaires, and affective measures**
  - **Baseline SPECT brain**
  - **Next day: Single HBOT**
  - **Repeat SPECT Brain (Neubauer Sequence)**
  - **39 HBOT's: 1.5 ATA/60 TDT, bid, 5d/wk.**
  - **Repeat testing and SPECT**
  - **If PBNR < 90%, 1 month break, then**
  - **40 HBOT's: 6/wk. (80 Rx total)**
  - **Repeat all above testing**
  - **6 month followup regarding return to work or school.**

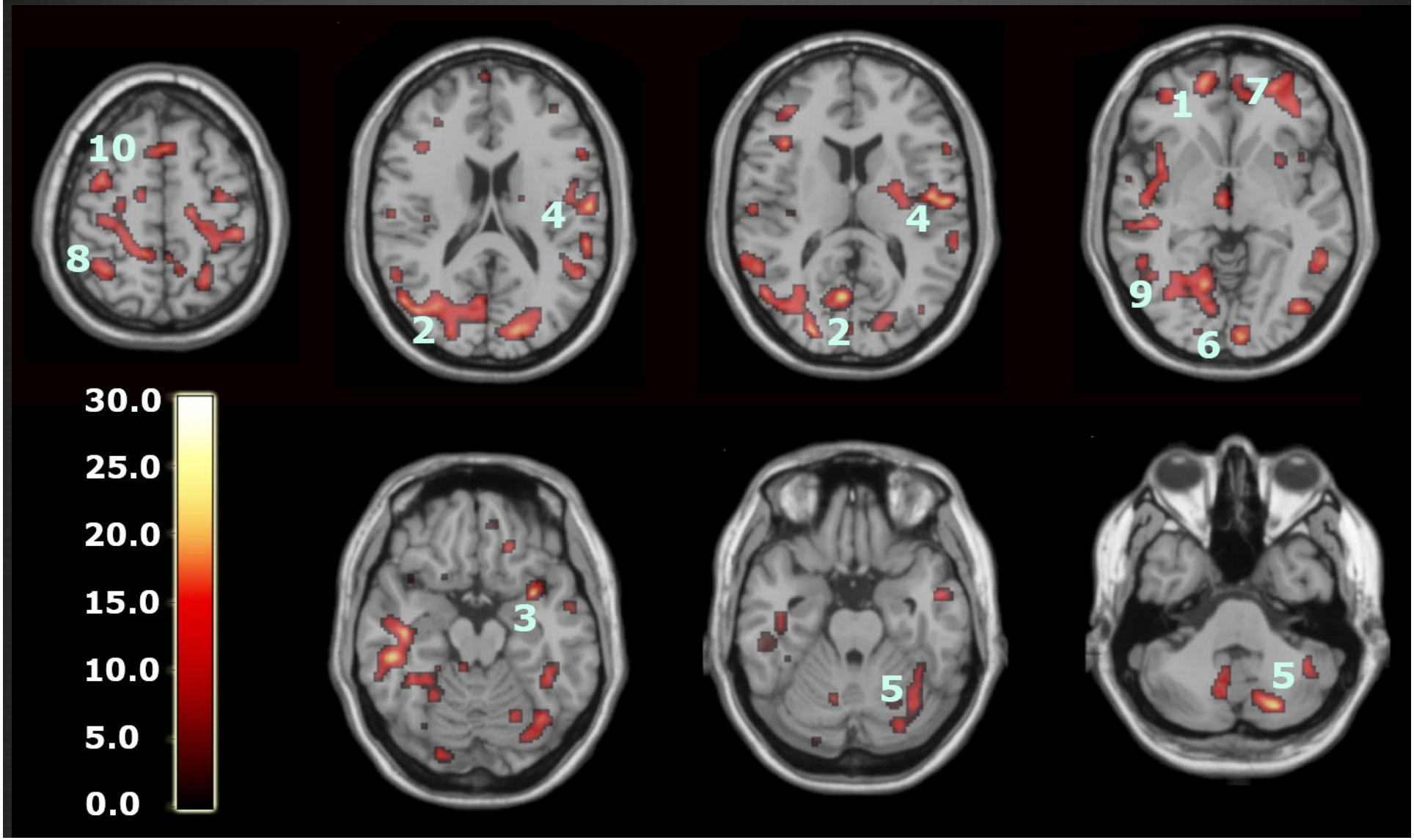
Patient Characteristics	% or actual number
Number of subjects	**16**
Sex	**all male**
Average age	**30** (21-45)
Average time from TBI to HBOT	**2.8 years** (1.25-4.75)
Average loss of consciousness	2 **min** (13 subjects: 1, 1-10 mins; 2 subjects: 4.5 & 9h-excluded from average)
Avg. # blast TBIs with LOC or altered LOC	**2.7 (1-7)**
Service at time of LOC	6.0 years (1-17)

Outcome Variables	Pre-HBOT Mean +/-SD (15) Median (Range)	Post-HBOT Mean +/-SD (15) Median (Range)	Pre:Post Diff +/-SD 95% CI	Signif of Pre to Post
Full Scale IQ	95.8 +/-8.4 98 (80-106)	110.6 +/-10.3 110 (97-129)	14.8 ± 7.4 CI: 10.7 to 18.9	p<0.001
Delayed Memory (WMS-IV)	97.7 ± 13.3 94 (76-125)	106.9 ± 15.4 107 (80-142)	9.2 ± 14.3 CI: 1.3 to 17.1	p=0.026
Rivermead Paragraph	9.5 ± 2.4 (15) 10 (6 – 14)	7.5 ± 3.6 (15) 8 (2 – 13)	-2.1 ± 3.7 CI: -4.1 to -0.0	p=0.049 **
Working Memory (WMS-IV)	97.0 ± 13.6 91 (85-131)	106.9 ± 13.1 105 (88-127)	9.9 ± 10.3 CI: 4.1 to 15.6	p=0.003
Stroop Color/Word Interference	84.3 ± 12.2 80 (65-108)	95.3 ± 12.8 94 (67-118)	11.1 ± 9.2 CI: 6.0 to 16.2	p<0.001
TOVA Inattention	73.3 ± 29.6 (15) 86 (40 – 107)	75.8 ± 27.2 (15) 85 (40 – 107)	2.5 ± 22.8 CI: -10.1 to 15.2	p=0.514
TOVA Impulsivity	89.6 ± 24.9 (15) 90 (40 – 123)	98.6 ± 23.1 (15) 107 (40 – 118)	9 ± 16.2 CI: 0.0 to 18.0	p=0.041
TOVA Reaction Time	93.1 ± 22.5 (15) 99 (53 – 120)	99.1 ± 14.6 (15) 103 (70 – 123)	5.9 ± 19.3 CI: -4.8 to 16.6	p=0.254
TOVA Variability	64.4 ± 28.7 45 (40-111)	75.3 ± 24.6 80 (40-111)	10.9 ± 20.2 CI: -0.2 to 22.1	p=0.045
FingerTap Dominant H	90.9 ± 18.3 (15) 93 (55 – 118)	98.6 ± 15.0 (15) 98 (75 – 130)	7.7 ± 20.7 CI: -3.8 to 19.2	p=0.174
FingerTap NonDominant	90.0 ± 21.5 (15) 95 (40 – 118)	94.0 ± 25.2 (15) 91 (40 – 130)	4 ± 18.5 CI: -6.2 to 14.2	p=0.416
Grooved Pegbrd Dom	88.9 ± 19.8 (15) 88 (55 – 124)	96.8 ± 18.8 (15) 98 (65 – 129)	7.9 ± 12.4 CI: 1.0 to 14.7	p=0.028
Grooved Pegbrd NonD	84.0 ± 22.0 (15) 85 (40 – 120)	87.3 ± 22.8 (15) 85 (40 – 118)	3.3 ± 15.3 CI: -5.2 to 11.8	p=0.423

**: Deterioration

Outcome Variables	Pre-HBOT Mean +/-SD (15) Median (Range)	Post-HBOT Mean +/-SD (15) Median (Range)	Pre:Post Diff +/-SD 95% CI	Signif of Pre to Post
Rivermead PCS	39.7 +/-6.0 40 (27-47)	24.1 +/-12.6 26 (0-42)	-15.6 ± 12.8 CI: -22.7 to -8.5	**p=0.0002**
PCL-M	67.4 ± 10.5 68 (48-84)	47.1 ± 16.0 46 (24-69)	-20.3 ± 18.2 CI: -30.4 to -10.2	**p<0.001**
PHQ-9 Depression	16.6 ± 4.9 18 (5-24)	8.2 ± 4.7 7 (2 - 17)	-8.4 ± 7.4 CI: -12.5 to -4.3	**p<0.001**
GAD-7 Anxiety	12.7 ± 5.8 14 (4-21)	7.9 ± 5.3 7 (0-21)	-4.8 ± 5.8 CI: -8.0 to -1.6	**p=0.007**
Perceived QOL	81 ± 37 74 (29-154)	114 ± 36 125 (42-161)	33 ± 36 CI: 13 to 53	**p=0.003**
% Back to N: Cognitive	49.7 ± 17.0 50 (20 – 85)	68.9 ± 20.0 75 (30 – 95)	19.2 ± 17.9 CI: 9.3 to 29.1	**p<0.001**
% Back to N: Physical	46.7 ± 22.2 45 (10 – 85)	67.5 ± 18.5 70 (25 – 90)	20.9 ± 16.3 CI: 11.8 to 29.9	**p<0.001**
% Back to N: Emotional	32.3 ± 19.9 30 (5 – 80)	63.2 ± 20.5 65 (30 – 90)	30.9 ± 21.7 CI: 18.8 to 42.9	**p<0.001**

Significant increases in blood flow after 40 HBOTs, p<0.001/voxel



Results of LSU Pilot Trial

- In one month of HBOT:
  - Significant improvement in symptoms
  - 15 point increase in full scale IQ
  - Significant increase in cognition
  - 30% decrease in PTSD; 8/14 no longer met criteria for PTSD
  - 51% reduction in depression
  - 38% reduction in anxiety
  - PBNR (cog., phys., emot.) +33-90%
  - 64% on psychoactive meds decreased or D/C'd medication, 1/9 increased analgesic medication
  - Significant improvement SPECT brain blood flow after 1 and 40 HBOTs

Harch, et al. J Neurotrauma, 2012:29(1):168-185.

Conclusions: HBOT in TBI/PTSD in Veterans

- This study reinforces studies by Neubauer and others.
- This study reinforces our experience with boxers and 22 years of experience in chronic TBI.
- Limitation: This study has no control group, however:
- Sensitivity analysis on the first 15 subjects shows that 50-75% of the measured improvements would have to be due to a placebo effect to lose significance of the findings.
- Imaging is inconsistent with known placebo effects.
- "These results cannot be explained by placebo effects."

Wolf, et al: U.S. Air Force Trial

- "Single-center, double-blind, sham-controlled"
  - 50 military service members, transported to San Antonio
  - ≥ 1 combat-related mTBI
  - 2.4 ATA oxygen/90 or 1.3-1.2 air/90, 30 Rxs, with two 10 minute air breaks, once/day, 5d/1d off, over 8 weeks.

    (Where did this protocol come from?)
  - ImPACT and PCL-M measured weekly and 6 weeks post treatment. Multiple other ouctome measurements.
  - Only symptom portion of ImPACT and the PCL-M reported.

Wolf, et al. J Neurotrauma, 2012; 29:2606–2612

U.S. Air Force Trial

- "Results:"
  - No significant difference post-Rx means on ImPACT or PCL-M between groups.
  - ImPACT total and PCL-M composite scores each showed significant improvement within groups.

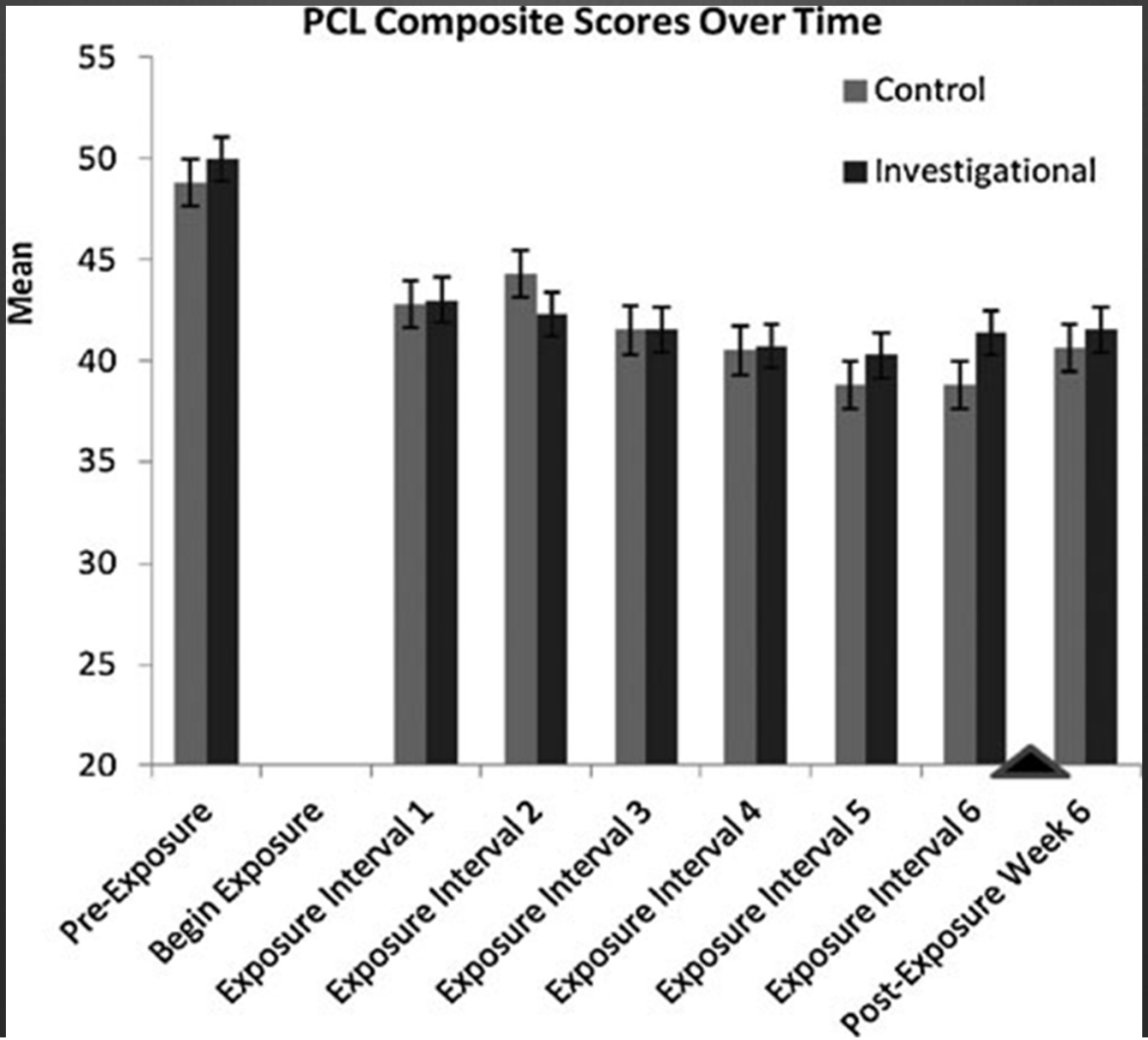
Conclusions:

"HBO_2 at 2.4 ATA pressure had no effect on post-concussive symptoms after mild TBI."

Wolf, et al. J Neurotrauma, 2012; 29:2606–2612

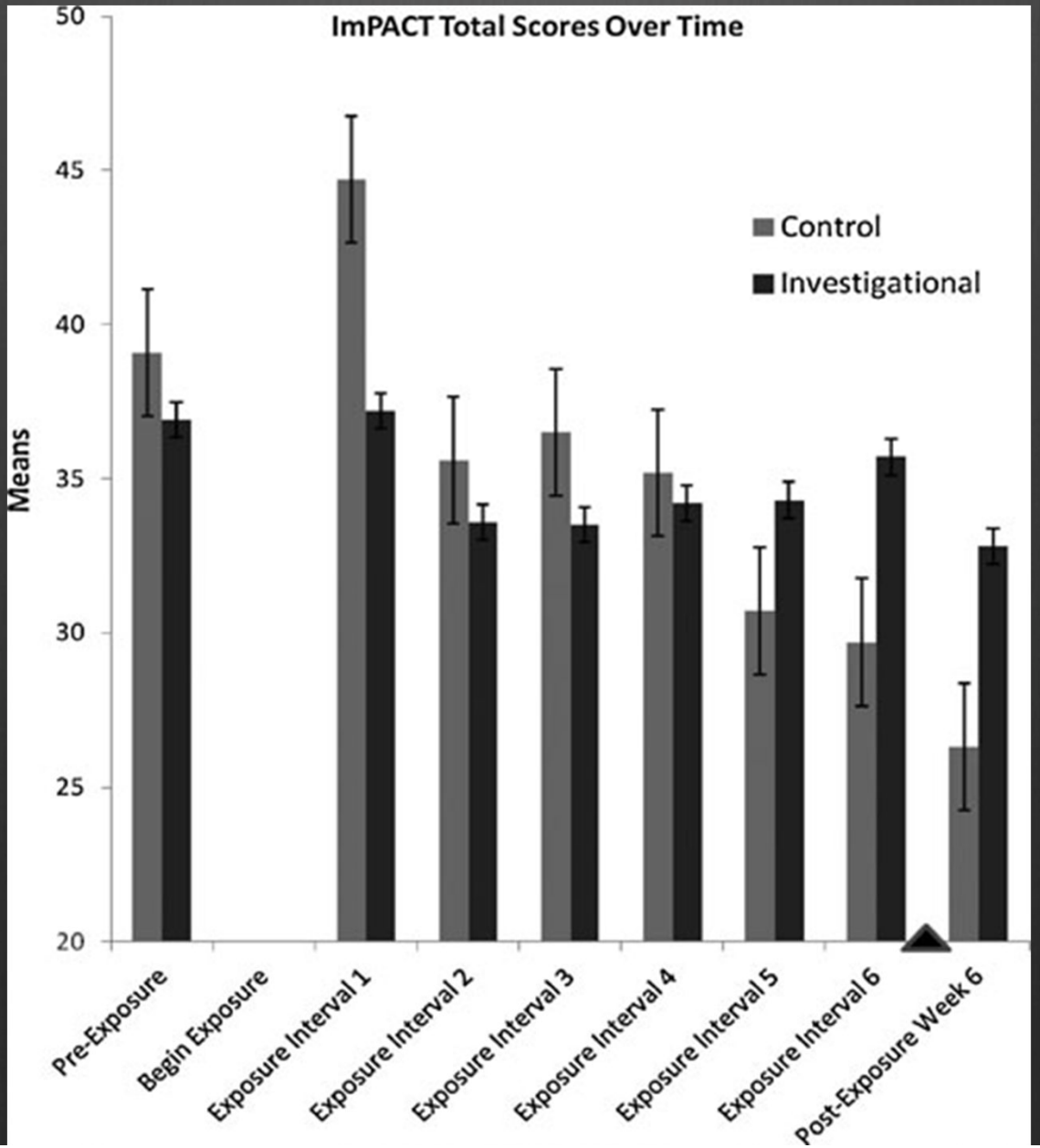
Let's look at the data:

Figure 1



Let's look at the data:

Figure 2



U.S. Air Force Trial

- More Accurate Conclusion based on the scientific definition of HBOT:
  - This is a comparative dosing study
  - U.S. war veterans with PPCS with or without PTSD experienced significant improvements in PPCS and PTSD symptoms with two different doses of HBOT.

Wolf, et al. J Neurotrauma, 2012; 29:2606–2612

Wolf, et al: U.S. Air Force Trial/Scorza Subset Analysis

- "Single-center, double-blind, sham-controlled"-Wolf study, 50 subjects, mTBI/PPCS:
  - Subset 1: PTSD screen "positive", PCL-M ≥ 50. + TBI
  - Subset 2: PTSD screen "negative", PCL-M < 45. + TBI
  - Analyze:
    - Subset 1 for decrease in PCL-M (> 10 point reduction clinically significant).
    - Subsets 1 and 2: ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing) symptom scores pre/post HBOT

Scorza, et al. UHMS ASM, 2013, oral presentation;abstract C27,

Wolf, et al: U.S. Air Force Trial/Scorza Subset Analysis

- Results:
  - Subset 1, PTSD + PPCS: Change in PCL-M scores

	Subset 1: PTSD + PPCS **Improved Not Impr/W**	**Subset 2: PPCS**
HBOT	10/13, 77% 3/13, 33%	?

	Subset 1: PTSD + PPCS	**Subset 2: PPCS**
"Sham"	"Min. diff. between groups"	???????
HBOT		"trend toward harm"

Wolf, et al: U.S. Air Force Trial/Scorza Subset Analysis

- Conclusions:
  - HBOT might be efficacious for PTSD symptoms.
    - Data implies that ”sham” is not beneficial for PTSD.
  - In patients with PPCS “improvements during HBO_2 may be secondary to treatment of concomitant PTSD, while HBO_2 may actually have a negative impact on isolated mTBI symptoms.”
  - Consistent w/ Harch, et al effects of HBOT on combined PPCS and PTSD.

Scorza, et al. UHMS ASM, 2013, oral presentation;abstract C27,

DARPA Cifu Navy Study
J Head Trauma Rehabil

- "Single-center, double-blind, sham-controlled"
  - 60 military service members, transported to Pensacola.
  - ≥ 1 combat-related mTBI
  - 3 Groups: 2.0 ATA pressure/.21, 1.5 ("anecdotal"—Harch Dose), or 2.0 ATA oxygen/60, once/day, 40 Rxs over 10 weeks.
  - Rivermead PCS Questionnaire and PCL-M pre and immediately post treatment, with multiple other outcome measures; only RPCSQ and PCL-M reported.

Cifu, et al. The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms. JHTR, 2012; 29:2606–2612

DARPA Cifu Navy Study J Head Trauma Rehabil

- Results:
- "Between-group testing: no significant differences on individual or total scores on the PCL-M or RPCSQ.
- Within-group testing: significant differences on several individual items for each group and 2.0 ATA oxygen group for PCL-M.

Cifu, et al. The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms. JHTR, 2012; 29:2606–2612

DARPA Cifu Navy Study J Head Trauma Rehabil

- Results:

O_2/Press.	PCL Pre	PCL Post	PCL Change	RPQ-16 (Total) Pre	RPQ-16 (Total) Post	RPQ Change
.21/2.0	45.14	43.9	- 1.24	32.81	32.86	+ 0.05
1.5/2.0	44.67	43.29	- 1.38	29.33	30.57	+ 1.24
2.0/2.0	49.39	42.56	- 6.83[a]	30.44	26.67	- 3.77

a. p= .05 (significant)

Cifu, et al. The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms. JHTR, 2012; 29:2606–2612

DARPA Cifu Navy Study J Head Trauma Rehabil

- Conclusion:
- "HBO_2 at either 1.5 or 2.0 ATA equivalent had no effect on PCS Sx after mTBI compared with sham compression."
- What about the PCL-M (PTSD) results in the 2.0 ATA oxygen group? Significant change. Not in the title, abstract conclusions, or conclusions of the main article.
- Essentially, no dose HBOT had an effect on PPCS, but one dose (2.0 ATA oxygen) was beneficial for PTSD in the setting of combined PPCS + PTSD.

Cifu, et al. The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms. JHTR, 2012; 29:2606–2612

DARPA Cifu Navy Study-

2nd Publication: Neurorehab & Neural Repair

- "Single-center, double-blind, sham-controlled"
  - Same study as JHTR article
  - Outcomes: computerized posturography, multiple neuropsychological tests.
  - Results: No immediate postintervention beneficial effect of 1.5 or 2.0 ATA O2 compared with the Sham Air intervention.
  - Conclusion: Do not support the use of HBO_2 to Rx cog., balance, or FM deficits asso. w/mTBI and PCS.

Walker, et al. Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention. *Neurorehabil Neural Repair June 2014 vol. 28 no. 5 420-432*

DARPA Cifu Navy Study

Neurorehab & Neural Repair

Let's have a look at the data. Statistical analysis done differently from the first publication on the same study and the Wolf, et al study

Walker, et al. Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention. *Neurorehabil Neural Repair June 2014 vol. 28 no. 5 420-432*

DARPA Cifu Navy Study

Neurorehab & Neural Repair

- 165 outcome measurements done on 55 different tests, 110 p values.
- ANOVA calculated for each test comparing the 3 different groups before and the 3 different groups after treatment.
- 106 of 110 ANOVA p values insignificant
- NO within group or between group comparisons on Treatment Effects.
- Essentially, NO TREATMENT EFFECTS WERE REPORTED!

DARPA Cifu Navy Study

Neurorehab & Neural Repair

- What happened?
- Let's take a look:

Table 1. Psychomotor Outcomes.

		Precompression			Postcompression		
Measure	n	Mean	SD	*P*	Mean	SD	*P*
Grooved Pegboard: dominant							
Sham Air	20	66.3	8.7	.15	67.5	7.5	.70
2.0 ATMO2	18	66.4	10.0		68.0	12.6	
1.5 ATMO2	20	72.2	12.9		70.4	13.9	
Grooved Pegboard: nondominant							
Sham Air	20	70.7	9.7	.54	72.5	11.5	.56
2.0 ATMO2	18	70.1	11.0		68.0	13.7	
1.5 ATMO2	20	74.3	15.7		71.5	13.8	
SOT Composite							
Sham Air	21	79.1	7.0	.37	77.0	9.5	.42
2.0 ATMO2	17	80.7	9.8		80.8	13.7	
1.5 ATMO2	19	76.4	10.2		75.7	12.5	

DARPA Cifu Navy Study

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Some tests appear to have significant change between groups

Recall	1.5 ATA			+2.6	**+31.0**
CVLT Index'd for Recognition	Sham Air	**.029***	.53	+0.2	+17.0
	2.0 ATA			-0.7	**-140.0**
	1.5 ATA			+1.8	**+78.0**
CVLT Short Delay Cue Recall	Sham Air	**.037***	.25	+0.6	+5.7
	2.0 ATA			+0.3	+2.4
	1.5 ATA			+2.7	**+27.0**
CVLT Recognition Total Hits	Sham Air	**.005***	.80	+0.1	+0.7
	2.0 ATA			-0.5	-3.4
	1.5 ATA			+2.2	**+18.0**
CPT-II Detectability	Sham Air	.16	.92	+0.03	+5.1
	2.0 ATA			+0.20	**+55.0**

DARPA Cifu Navy Study

Neurorehab & Neural Repair

Other tests show unidirectional improvement for all groups

PASAT 2.4 Second							
Sham Air	19	33.3	14.4	.96	39.6	12.9	.72
2.0 ATMO2	13	32.6	12.4		39.6	14.6	
1.5 ATMO2	18	31.9	14.2		36.4	12.6	
PASAT 1.6 Second: discontinuance rate							
Sham Air	19	26%		.58	16%		.59
2.0 ATMO2	13	23%			15%		
1.5 ATMO2	18	39%			28%		
PASAT 1.6 Second							
Sham Air	14	27.4	12.7	.77	31.7	12.3	.69
2.0 ATMO2	10	28.7	5.7		35.0	8.9	
1.5 ATMO2	11	25.6	9.4		32.2	8.0	
PASAT 1.2 Second: Discontinuance Rate							
Sham Air	19	32%		.72	26%		.70
2.0 ATMO2	13	38%			15%		
1.5 ATMO2	18	44%			28%		
PASAT 1.2 Second							
Sham Air	13	21.1	9.8	.92	23.3	10.4	.73
2.0 ATMO2	8	22.0	4.6		25.8	8.1	
1.5 ATMO2	10	20.5	6.6		23.2	8.5	
BVMT-R Discrimination Index							
Sham Air	19	5.6	0.6	.28	4.2	2.5	.85
2.0 ATMO2	13	5.8	0.4		4.5	2.2	
1.5 ATMO2	18	5.8	0.4		4.6	2.3	

DARPA Cifu Navy Study

Neurorehab & Neural Repair

Other tests show unidirectional improvement for all groups

BVMT-R Discrimination Index							
Sham Air	19	5.6	0.6	.28	4.2	2.5	.85
2.0 ATMO2	13	5.8	0.4		4.5	2.2	
1.5 ATMO2	18	5.8	0.4		4.6	2.3	

BVMT-R Discrimination Index	Mean, pre	Mean, post	Change	Standard Deviation	change
"Sham air"	5.6	4.2	-1.4	2.5	-25%
2.0 ATMO2	5.8	4.5	-1.3	2.2	-22%
1.5 ATMO2	5.8	4.6	-1.2	2.3	-21%

DARPA Cifu Navy Study

- True Conclusion:
  - Odd statistical analysis.
  - Within group between group treatment effects not measured.
  - Variety of changes on tests per group and unidirectional changes for some tests.
  - Data suggests different effects of different doses of HBOT.
  - Hard to draw conclusions from the study.
  - Assume the three doses have neutral effects on cognitive, balance, or fine motor deficits in subjects with mTBI PPCS.

Walker, et al. Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention. *Neurorehabil Neural Repair June 2014 vol. 28 no. 5 420-432*

DARPA Cifu Navy Study

3rd Publication: Annals of Neurology

- "Single-center, double-blind, sham-controlled"
  - Same study as JHTR and NNR article
  - Outcomes: RPCSQ, functional, cognitive, & psychomotor outcomes at 3 months post treatment.

- Results: The interaction of time by intervention group was not significant for improvement on the RPQ-16. Nor was there evidence of efficacy on the RPQ-16 for any subgroup. No significant time by intervention interaction was found for any functional, cognitive, or psychomotor secondary outcome measure at an unadjusted 0.05 significance level. TRANSLATION: HBOT DID NOT WORK.

Cifu, et al. **Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes.** Ann Neurol. 2014 Feb;75(2):277-86.

DARPA Cifu Navy Study

Annals of Neurology

- Conclusion: " Using a randomized control trial design and analysis including a sham, results showed no evidence of efficacy by 3 months post-compression to treat the symptomatic, cognitive, or behavioral sequelae of PCS after combat-related mTBI."
- LET'S TAKE A CLOSER LOOK!

Cifu, et al. **Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes.** Ann Neurol. 2014 Feb;75(2):277-86.

Another odd statistical analysis, different from the original Wolf study and the first publication on this study.

The F Test =

$$\frac{\text{Variance between Rx}}{\text{Variance within Rx}}$$

Essentially there is no comparison effects of "sham" to the other groups.

http://en.wikipedia.org/wiki/Analysis_of_variance#The_F-test

TABLE 2. Explanatory Variable Main Effects on Rivermead Post-Concussion Questionnaire-16

Explanatory Variable	*F*-Ratio (*df*1, *df*2)	*p*
Time	0.9 (2, 55.5)	0.426
Intervention group	0.5 (2, 47.2)	0.590
Blast exposure	2.6 (1, 48.2)	0.112
PTA	4.8 (1, 48.4)	0.033[a]
LOC	0.9 (1, 48.1)	0.350
PTSD	7.3 (1, 48.5)	0.009[a]
Injury elapse	2.4 (1, 48.3)	0.131
Alcohol use	1.5 (1, 129)	0.219
Age	0.0 (1, 50.1)	0.925
Previous head injury	0.0 (1, 48.1)	0.937
McGill	33.4 (1,143)	<0.001[a]
WTAR	1.2 (1,119)	0.278
TOMM	0.1 (1, 47.7)	0.730

TABLE 3. Hypothesis Tests for the Treatment by Time Interaction for the Secondary Outcomes

Predictor	*F*-Ratio (*df*1, *df*2)	*p*
RPQ-3	0.7 (4, 64.0)	0.592
RPQ-13	1.0 (4, 63.8)	0.400
Mayo	0.6 (4, 62.8)	0.702
Balance, SOT	1.0 (4, 58.9)	0.443
WAIS	1.8 (4, 59.4)	0.141
Trail-Making B	0.7 (4, 64.9)	0.621
Stroop	0.6 (4, 60.2)	0.664
CPT-II	0.6 (4, 60.9)	0.685
CVLT Long Delay Free Recall	0.8 (4, 63.1)	0.523
PASAT	1.4 (4, 52.9)	0.256
BVMT Delay Recall	0.5 (4, 62.3)	0.753
COWAT	1.6 (4, 64.1)	0.197
Grooved Peg Board	0.5 (4, 47.5)	0.724
SWLS	0.5 (4, 61.2)	0.751
Depression, CESD	0.5 (4, 63.8)	0.767
GOSE	0.8 (4, 57.7)	0.503

DARPA Cifu Navy Study

Annals of Neurology-Results Section:

Although not relevant to assessing intervention efficacy, some secondary outcome analyses did show significant effect(s) with 1 or more explanatory variables similar to the primary outcome. The following secondary measures demonstrated statistically significant changes irrespective of treatment. Improvements were shown on Trails B (at 12weeks), CVLT (at 2 weeks), PASAT (at 2 and 12 weeks), BVMT (at 12 weeks), and COWAT (at 2 and 12 weeks), whereas WAIS-III working memory worsened (at 2 weeks). No significant changes were noted on any of the other secondary outcome measures. Complete results of the effects are shown in Supplementary Tables A1 to A17. Let's See!

DARPA Cifu Navy Study

Annals of Neurology

Supplementary Tables A1 to A17

(a separate download).

- Baseline measurements were lower than the 2 week (d=0.49, SE=0.21, 95%CI=0.07, 0.90) and 12 week (d=0.78, SE=0.21, 95% CI: 0.36, 1.20) measurements.

That means that memory improved with Treatment (1.5 and 2.0 ATA?)

Table A6: WAIS-III Working Memory Index

Predictor	F-ratio(df1, df2)	*P*
Time	**6.8 (2, 52.8)**	**0.002**
Treatment	2.0 (2, 39.1)	0.145
Blast Exposure	3.5 (1, 41.5)	0.067
PTA	0.0 (1, 40.3)	0.995
LOC	0.3 (1, 40.7)	0.605
PTSD	2.7 (1, 42.1)	0.106
Injury Elapse	1.4 (1, 24.9)	0.245
Alcohol Use	0.8 (1, 138)	0.367
Age	0.0 (1, 42.3)	0.989
Previous Head Injury	0.1 (1, 39.7)	0.742
McGill	1.5 (1,119)	0.222
WTAR	**11.3 (1, 108)**	**0.001**
TOMM	1.2 (1, 40.4)	0.279
Time*Treatment	1.8 (4, 59.4)	0.141

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Supplementary Tables A1 to A17

Same findings for

1. Trails B ($p<0.001$)
2. CVLT Long Delayed Recall (Delayed Memory) ($p=0.017$)
3. PASAT 2.0 second pacing (sustained auditory attention) ($p<0.001$)
4. BVMT Delayed Recall (Visual Delayed Memory) ($p=0.001$)
5. COWAT Letter Fluency (Verbal Fluency) ($p<0.001$)

Essentially, 6 cognitive tests showed improvement at 3 months (irrespective of group. ? Participation effect? Delayed HBO effect?)

DARPA Cifu Navy Study

Annals of Neurology

So, what are the true results of the Cifu Annals of Neurology paper?

Did hyperbaric therapy have any effect or not?

By the data, no treatment effects were ever measured and the conclusions are predicated on the 2.0 ATA/normoxic air group as sham.

TRUE CONCLUSION:

Cifu, et al is a multidosing study of 3 doses of hyperbaric therapy in which the statistical analysis renders it impossible to tell if there was any treatment effect of any dose of hyperbaric therapy. Treatment compared to "sham" was not done.

Boussi-Gross Israeli Study

- 56 civilian mTBI PPCS, 1-5 years post injury (avg. ~2.8 yrs.)
- Randomized, crossover (control group)-everyone gets HBOT.
- No Sham pressure group.
- HBOT 1.5/60, qd, x 40.
- "Mindstreams" computer cognitive testing, QoL, SPECT, pre, immediately post control and Rx.

Boussi-Gross R, et al. (2013) Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial. PLoS ONE 8(11): e79995.

Boussi-Gross Israeli Study

- Results:
  - Significant improvement in cognitive function and QoL in both groups following HBOT.
  - No significant improvement following control period.
  - SPECT revealed elevated brain activity in good agreement with the cognitive improvements.
- Conclusions:
  - HBOT can induce neuroplasticity leading to repair of chronically impaired brain functions and improved QoL in mTBI patients with PPCS at late chronic stage.
  - Implied conclusion: 1.5 ATA HBOT is beneficial in civilian PPCS.

Significant dropouts: 7/31 in Crossover Group, 4/36 in HBOT, for a variety of reasons. Additional dropouts not accounted for in final tally.

Boussi-Gross R, et al. (2013) Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial. PLoS ONE 8(11): e79995.

Miller, et al, MRMC Multi-Center Trial: 1.5 ATA HBO_2 vs. Sham vs. Routine TBI Care

- Military subjects, PCS > 4 mos. post TBI , RCT.
- 4 sites: Fort Carson, Camp Lejeune, Camp Pendleton and Fort Gordon
- **HBOT Dose:**
  - 1.5 ATA O_2/60 min X 40, 10 weeks, + TBI care
  - "Sham:" 1.2 ATA air/60 min X 40, 10 weeks, + TBI care
  - "Comparator:" Routine TBI care
  - Outcomes: measured pre and post HBOT & at 10 weeks. Primary: 2 point change on RPQ-3., secondary: NSI +
    - **PTSD Symptoms: PCL–C (self-report questionnaire)**
    - Sleep, pain, depression and anxiety symptoms
    - **QoL questionnaires.**
    - Neurologic exam
    - ANAM (automated cognitive function battery)
    - Cognitive Test Battery

Miller, et al. JAMA Intern Med. Doi: 10.1001/jamainternmed.2014.5479

Miller, et al, MRMC Multi-Center Trial:
1.5 ATA HBO_2 vs. Sham vs. Routine TBI Care

- Results: Intention to Treat Analysis
  - Change Scores, within group:

	RPQ-3 Change	p value	% meeting 2 point change
Control	0.0	.97	25%
HBOT	-1.2	.04	52%*
"Sham"	-1.5	.03	33%*

No p value comparison of "sham" or HBO to Control. Only compared "Sham" to HBO (p=.24)

	RPQ Total	p value	NSI	p value	PCL-C	p value
Control	-.5	.91	+ 1.1	?	-2.1	?
HBOT	- 5.4	.008	- 3.7	?	-5.0	?
"Sham"	- 7.0	.02	- 6.9	?	-11.4	?

P for NSI: "These change scores were not significantly different (p = .49). No within group p values as done for RPQ. P for PCL: no p values; "PTSD Sx improved, favoring sham over HBO group.'

"Favorable change scores on the total RPQ were higher for the HBO group (?) but no difference between the HBO group and the sham group was observed (p=.70)"

Miller, et al, MRMC Multi-Center Trial:
1.5 ATA HBO_2 vs. Sham vs. Routine TBI Care

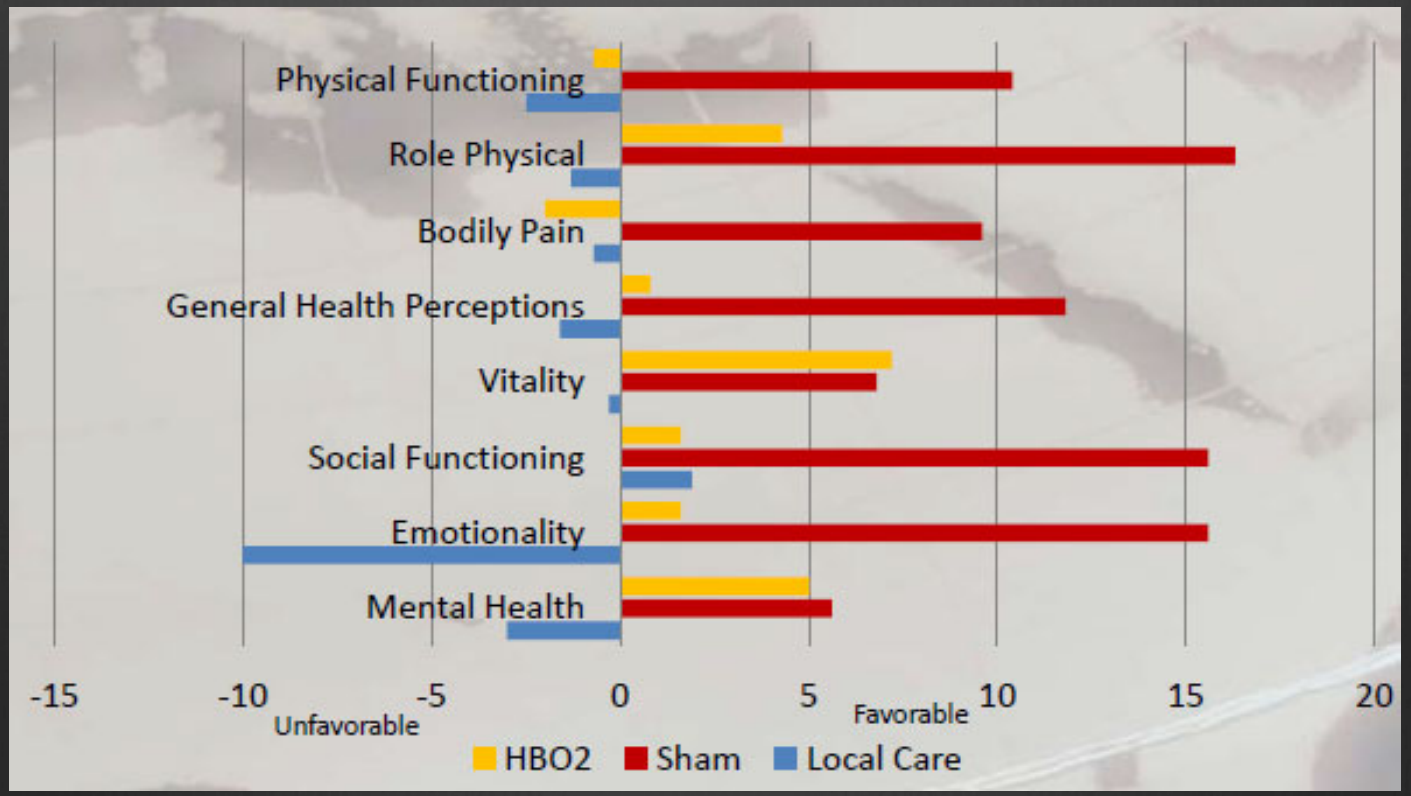
- Results: Intention to Treat Analysis
  - "Patient reported outcomes of depression, general anxiety, pain, sleep, …health-related QoL… improved favoring the "sham" group over the HBO group" for nearly all measures.
  - "No statistical differences were observed between the 2 treatment groups at baseline or on change from baseline scores in any of the cognitive testing measured by the ANAM…"
- Let's look at a representative example of the rest of the data:

Slides courtesy of Col. R. Scott Miller, M.D.

Health Related Quality of Life

Short Form 36 Health Survey

Change from Baseline – Health Concepts (ITT)



- Also no difference between HBO2 and sham on Satisfaction with Life Scale with both showing modest improvement

Summary by Authors, Miller, et al:

- In this study, standard local care offered no improvement during the 3 month observation period
- Randomization to the chamber (either sham or placebo) offered statistical and in some measures clinically significant improvement over local routine TBI care
  - "This explains the anecdotal findings reported."
- ***"Hyperbaric oxygen at 1.5 ATA for 40 sessions" offered no statistical benefit over sham in immediate relief of PCS symptoms ."***
  - ***"Observed improvements were not oxygen-mediated, but may reflect non-specific improvements related to placebo effects." (The "ritual" argument).***

However,

- Results:
  - Improvement on every outcome measure for 1.2 and 1.5 ATA
  - Generally greater improvement 1.2 ATA air.
  - Difference in outcome between all groups for every measure

- Conclusions:
  - "We believe it is biologically implausible that air at 1.2 ATA has a beneficial effect on healing the damaged brain remotely after mTBI. (Belief System Argument).
  - If the Belief System Argument why did the placebo and ritual in the Cifu studies not produce the same positive data? Suggests effects of different doses.

Miller RS. JAMA Intern Med. Doi: 10.1001/jamainternmed.2014.5479, 11/17/2014.

HBOT in Persistent Post-Concussion Syndrome: Clinical Literature Review

Harch, et al. Med Gas Res, 2017;7(3):156-174.

Full Data of LSU Pilot Trial: 30 subjects, 1 dropout
Data analysis on 29 subjects: 26 with TBI/PTSD, 3 TBI
29 matched controls for imaging portion
6 month phone fullowup.

Results using protocol we developed in 1990:

1. Significant Improvement: Sx, PEx, cognition, affective measures, SPECT.
2. Reduction in psychoactive medication use.
3. Abnormal SPECT compared to controls.
4. 75% normalization of abnormal SPECT ROIs post HBOT.
5. 52% of subjects no longer met PCL-M criteria for PTSD.
6. 83% of subjects with suicidal ideation no longer expressed suicidal thoughts after HBOT (the only study to date in veterans reporting reduction in suicidal ideation…see "Suicide Epidemic."

HBOT in Persistent Post-Concussion Syndrome: Clinical Literature Review

Harch, et al. Med Gas Res, 2017-Case Control

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

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

Six month follow-up: Further improvement in Sx.

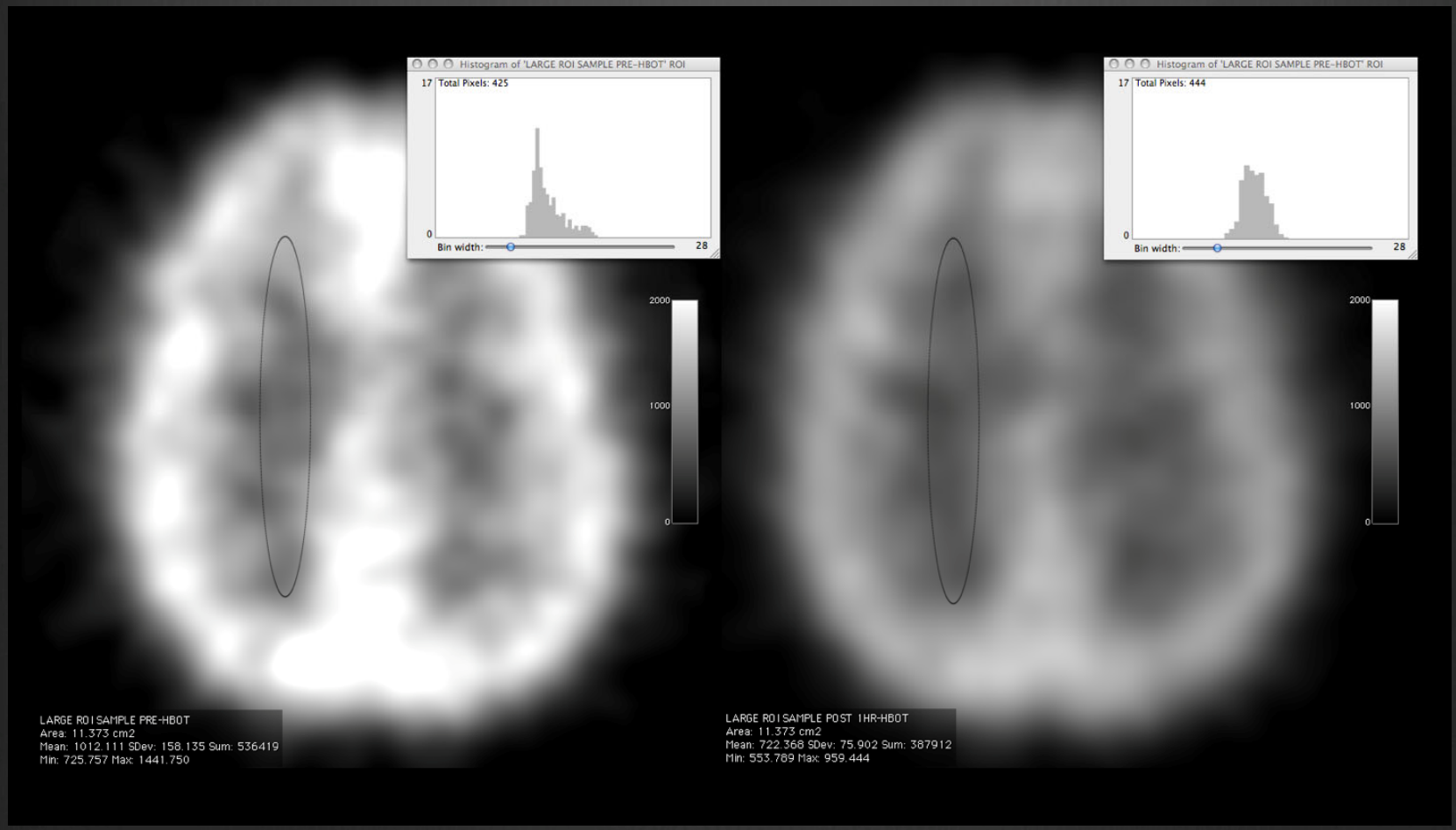
HBOT in Persistent Post-Concussion Syndrome: Clinical Literature Review

Harch, et al. Med Gas Res, 2017-Case Control

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

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

SPECT Analysis



HBOT in Persistent Post-Concussion Syndrome: Clinical Literature Review

Harch, et al. Med Gas Res, 2017-Case Control

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

Region of interest	Mean counts/pixel (MCP)			Coefficient of Variation (CV)		
	Pre	Post 1	Post 40	Pre	Post 1	Post 40
Left Gray 030	0.374 (–218 – 83)	0.775 (–165 – 124)	0.175 (–256 – 48)	0.647 (–0.52 – 0.83)	*(+) 0.086 (–1.06 – 0.07)*	0.445 (–0.85 – 0.38)
Left Gray 060	0.251 (–248 – 66)	0.491 (–192 – 93)	0.134 (–277 – 38)	0.708 (–0.54 – 0.79)	0.223 (–1.10 – 0.26)	*(+) 0.070 (–1.18 – 0.05)*
Left Gray 090	0.640 (–188 – 116)	0.629 (–107 – 176)	0.658 (–196 – 125)	0.310 (–1.32 – 0.43)	**(+) 0.025 (–1.68 to –0.12)**	0.176 (–1.33 – 0.25)
Left Gray 120	0.441 (–214 – 95)	0.785 (–127 – 167)	0.273 (–245 – 71)	0.783 (–0.76 – 0.58)	0.139 (–1.24 – 0.18)	0.347 (–1.14 – 0.41)
Left Gray 150	0.562 (–229 – 125)	0.890 (–140 – 161)	0.510 (–224 – 112)	**(–) 0.041 (0.03 – 1.57)**	0.966 (–0.64 – 0.67)	0.428 (–0.50 – 1.17)
Left Gray All	0.428 (–214 – 92)	0.988 (–141 – 139)	0.304 (–236 – 75)	0.594 (–0.30 – 0.51)	**(+) 0.034 (–0.89 to –0.04)**	0.183 (–0.68 – 0.13)
Left White 060	0.104 (–227 – 22)	0.410 (–70 – 168)	0.336 (–198 – 69)	0.427 (–0.80 – 1.87)	0.864 (–1.14 – 1.35)	0.997 (–1.28 – 1.28)
Left White 120	*(–) 0.074 (–232 – 11)*	0.715 (–90 – 130)	0.147 (–223 – 34)	**(–) 0.013 (0.29 – 2.36)**	0.348 (–0.48 – 1.35)	0.638 (–0.83 – 1.35)
Left White All	*(–) 0.083 (–228 – 14)*	0.534 (–76 – 146)	0.219 (–207 – 48)	**(–) 0.043 (0.03 – 1.82)**	0.477 (–0.48 – 1.02)	0.773 (–0.76 – 1.01)
Right Gray 030	0.457 (–215 – 98)	0.724 (–175 – 122)	0.219 (–265 – 62)	0.891 (–0.50 – 0.57)	0.291 (–0.81 – 0.25)	0.370 (–0.77 – 0.29)
Right Gray 060	0.128 (–284 – 36)	0.360 (–211 – 78)	*(–) 0.064 (–317 – 9)*	0.959 (–0.65 – 0.62)	0.149 (–1.08 – 0.17)	0.174 (–1.03 – 0.19)
Right Gray 090	0.314 (–231 – 75)	0.783 (–157 – 119)	0.331 (–247 – 85)	0.190 (–0.22 – 1.07)	0.718 (–0.55 – 0.79)	0.121 (–0.14 – 1.16)
Right Gray 120	0.165 (–253 – 44)	0.724 (–169 – 118)	0.268 (–263 – 75)	0.175 (–0.20 – 1.08)	0.958 (–0.69 – 0.66)	0.186 (–0.19 – 0.94)
Right Gray 150	0.376 (–224 – 86)	0.666 (–182 – 117)	0.508 (–227 – 114)	**(–) 0.005 (0.29 – 1.53)**	**(–) 0.020 (0.12 – 1.29)**	**(–) 0.047 (0.01 – 1.18)**
Right Gray All	0.253 (–237 – 63)	0.628 (–174 – 106)	0.234 (–260 – 65)	**(–) 0.012 (0.08 – 0.64)**	0.928 (–0.31 – 0.34)	0.245 (–0.12 – 0.44)
Right White 060	*(–) 0.075 (–233 – 12)*	0.917 (–126 – 113)	0.100 (–237 – 21)	**(–) 0.010 (0.39 – 2.68)**	0.407 (–0.76 – 1.84)	0.557 (–0.83 – 1.52)
Right White 120	**(–) 0.027 (–267 to –17)**	0.799 (–126 – 98)	*(–) 0.067 (–250 – 9)*	**(–) 0.002 (0.61 – 2.55)**	0.114 (–0.18 – 1.64)	**(–) 0.030 (0.11 – 2.20)**
Right White All	**(–) 0.037 (–244 to –8)**	0.854 (–122 – 101)	*(–) 0.074 (–240 – 12)*	**(–) <0.001 (0.84 – 2.27)**	0.109 (–0.15 – 1.42)	*(–) 0.036 (–0.11 – 1.61)*

HBOT in Persistent Post-Concussion Syndrome: Clinical Literature Review

Harch, et al. Med Gas Res, 2017-Case Control

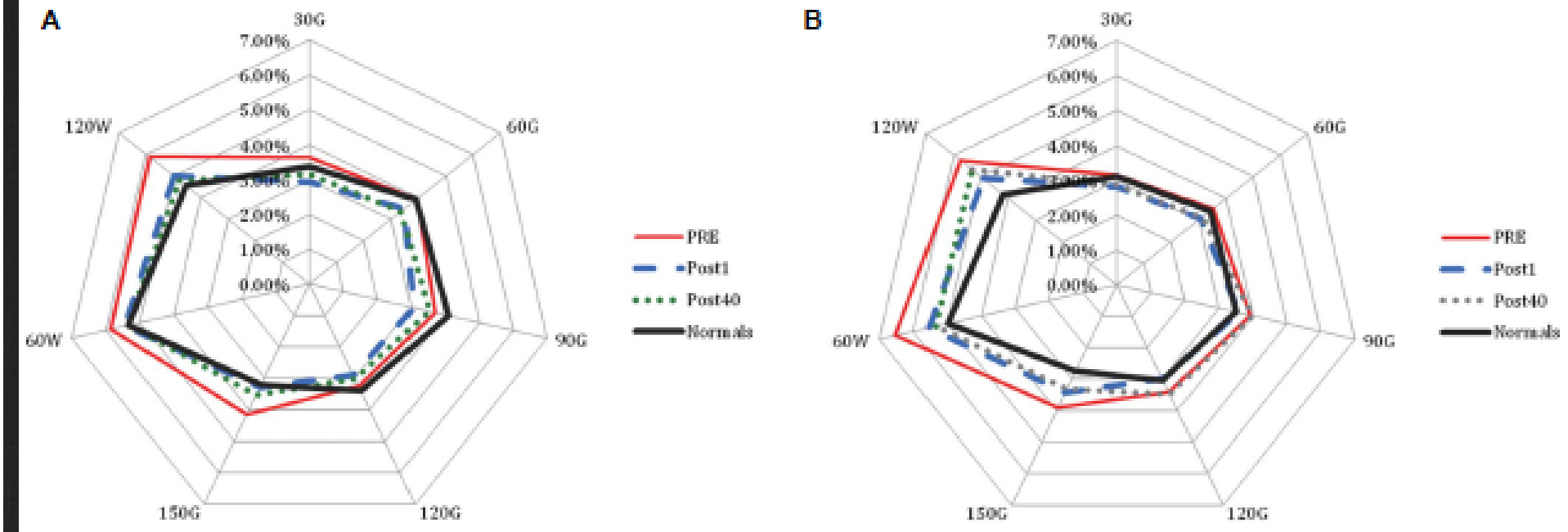


Figure 2: Radar graph of left (A) and right (B) hemisphere.

HBOT in Persistent Post-Concussion Syndrome: Clinical Literature Review

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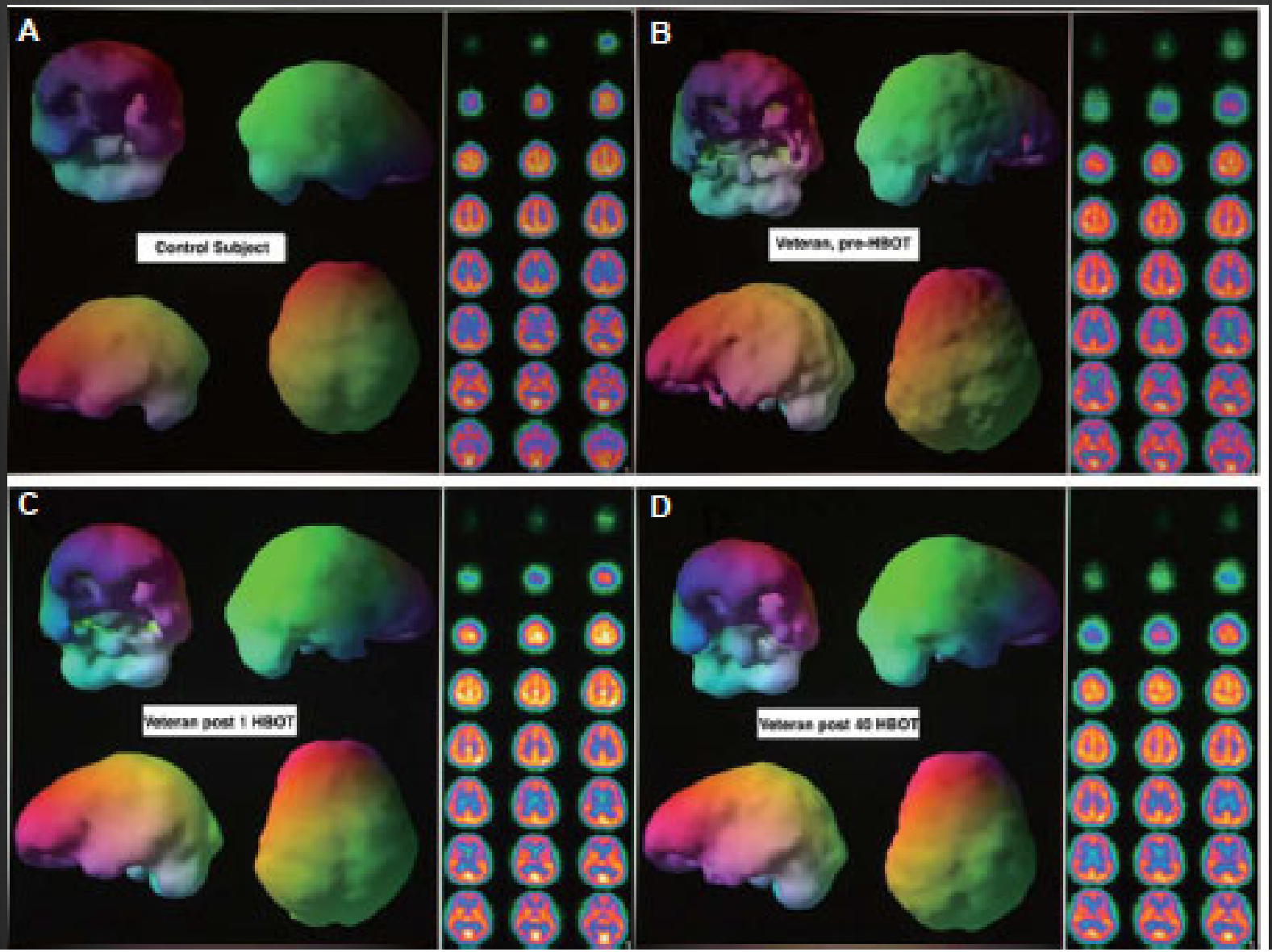


HBOT in Persistent Post-Concussion Syndrome: Clinical Literature Review

Harch, et al. Med Gas Res, 2017-Case Control

Conclusions :

1. Significant improvements in PPCS and PTSD symptoms, physical exam abnormalities, cognition, depression, anxiety, quality of life, and brain blood flow.
2. Further symptom improvement after 6 months.
3. Compared to Controls: brain blood flow abnormal and nearly statistically indistinguishable from Controls after HBOT.
4. Blood flow abnormalities and improvements in blood flow after HBOT were in the white matter, the primary site of TBI.
5. Significant reduction in anxiety: 52% no longer met criteria for PTSD.
6. Significant reduction in suicidal ideation.
7. Significant reduction in psychoactive medication.
8. Best Evidence-Based Medicine for combined PPCS and PTSD.

BIMA: Weaver, et al. UHM, 2018;45(2):129-156

- RCT: 71 U.S. military subjects with PPCS 3 months-5 years post TBI
- Rx: multiplace at 3 sites: Washington, Ft. Carson, Camp Lejeune. Assessments done at local sites, but most at Colorado Springs Assessment Center.
  - HBOT: 1.5 ATA/60 at depth x 40/12 weeks
  - "Sham:" 1.2 ATA/60 air x 40/12 weeks.
- Outcomes pre, 1 week post Rx (13 weeks), 3 months post Rx, and 9 month phone followup:
  - Sx, neuropsychological testing, neurological, electroencephalography, sleep, auditory/vestibular, electrocardiography, vision, neuroimaging, and laboratory measures.

BIMA: Weaver, et al. UHM, 2018;45(2):129-156

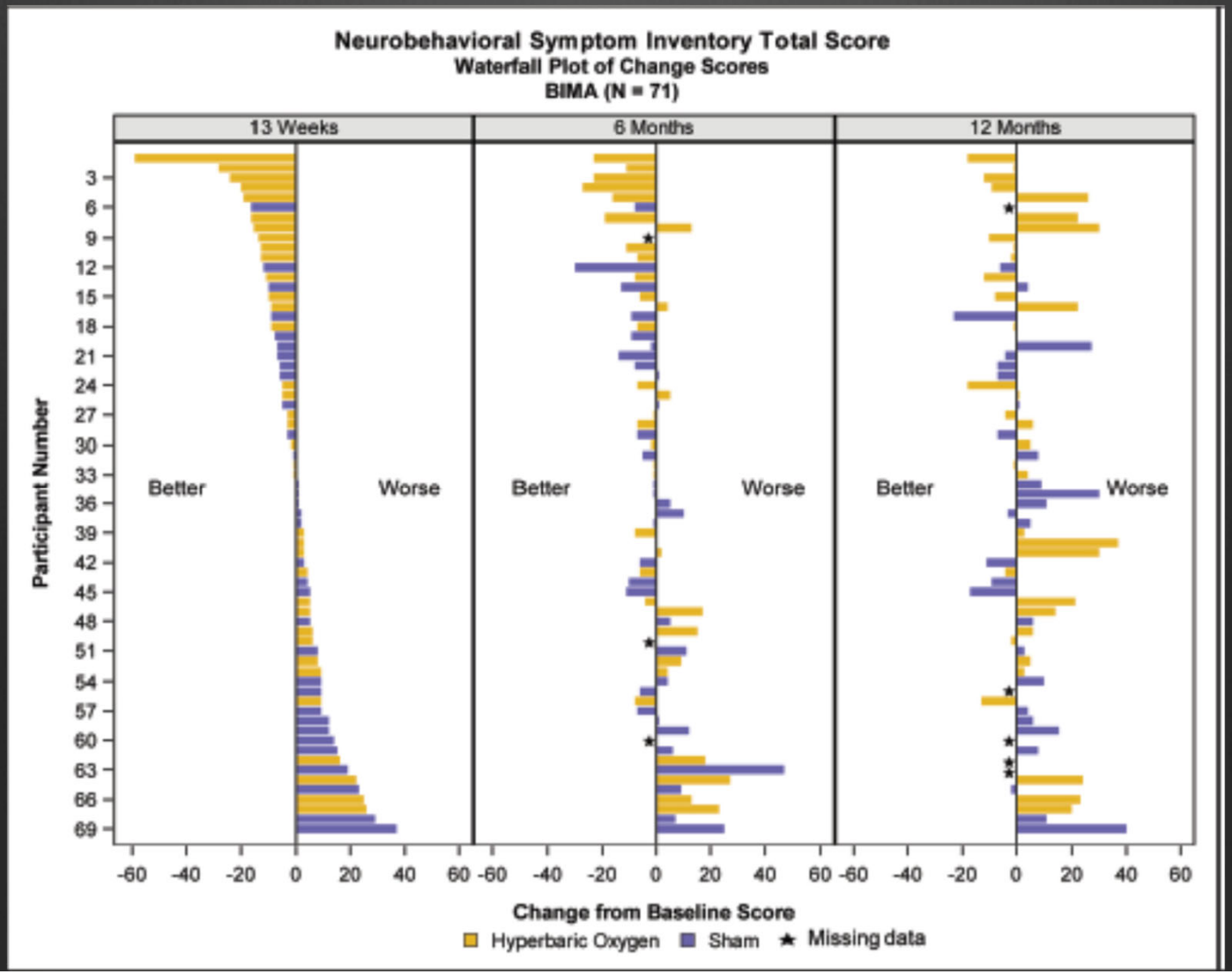
- Results: massive data.
- NSI: HBO2 group had improved 13-week scores (mean change -3.6 points,P=0.03) compared to sham (+3.9 points).
- NSI in patients with PTSD: change with HBO2 was more pronounced (-8.6 vs. +4.8 points with sham, P=0.02).
- PTSD symptoms improved in HBO2 group, and more so in the subgroup with PTSD.
- Improvements regressed at 3 and 9 months post treatment.

BIMA: Weaver, et al. UHM, 2018;45(2):129-156

- HBO2 improved some cognitive processing speed and sleep measures.
- HBO2 improved functional balance and reduced vestibular complaints at 13 weeks in patients with PTSD.
- **Conclusions**:
- HBO2 at 1.5 ATA improved PCS and PTSD symptoms, cognitive processing speed, sleep quality, balance function, most dramatically in those with PTSD.
- Changes did not persist beyond three months post treatment.

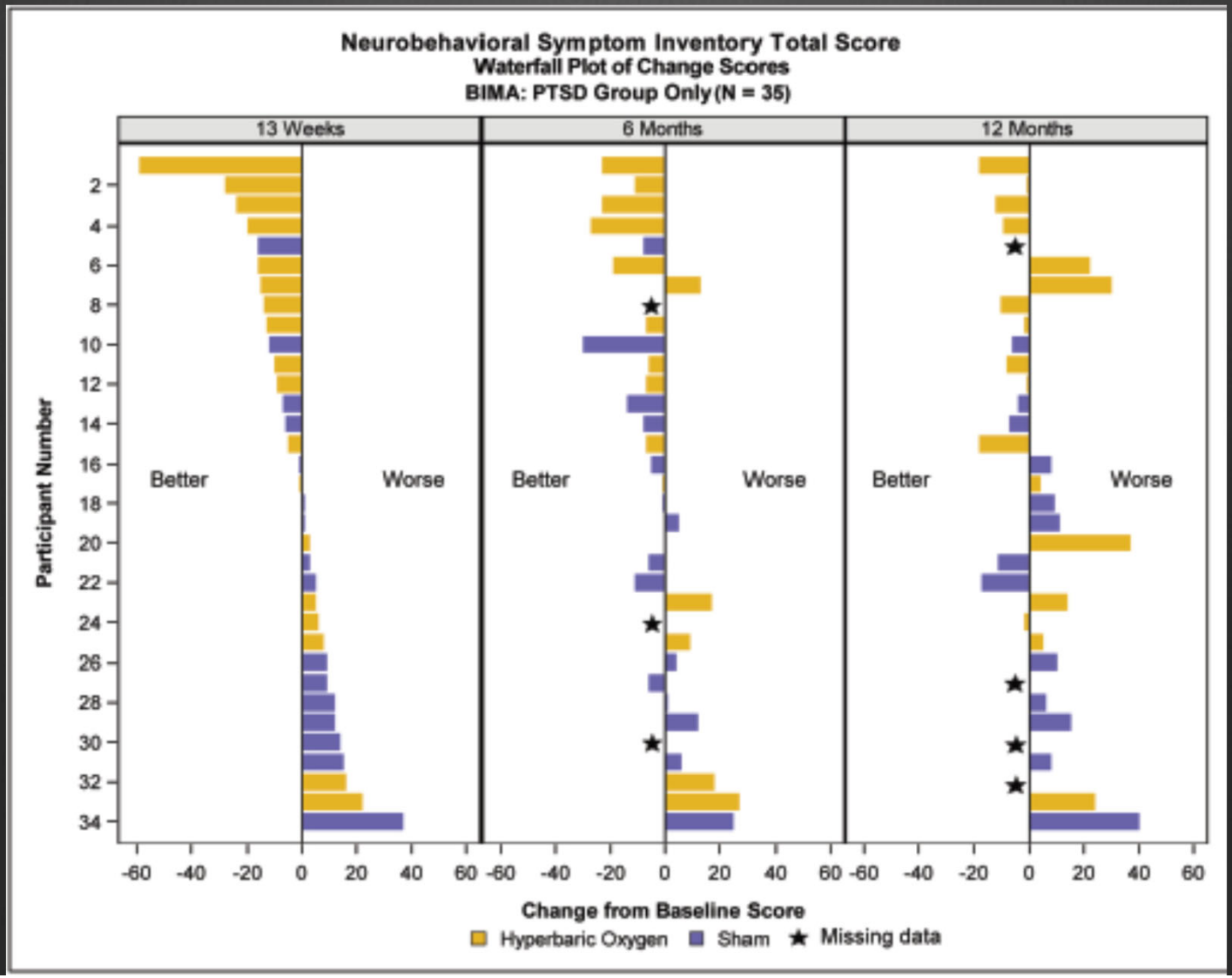
BIMA: Weaver, et al. UHM.

NSI: All subjects

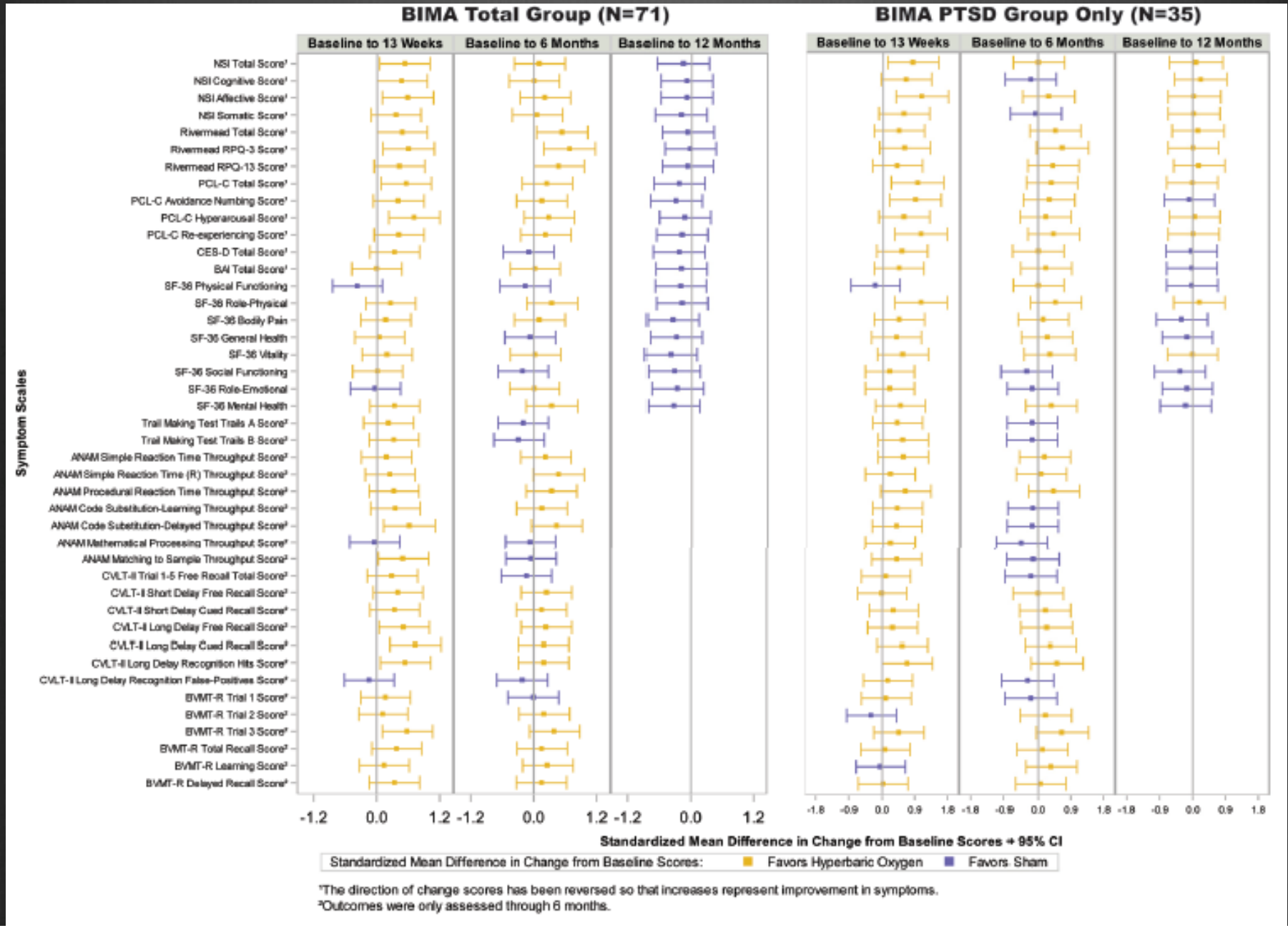


BIMA: Weaver, et al. UHM

NSI: PTSD Subjects



BIMA: Weaver, et al. UHM. Additional Outcomes



¹The direction of change scores has been reversed so that increases represent improvement in symptoms.
²Outcomes were only assessed through 6 months.

Harch, et al, LSU RCT: IRB #7381 HBOT in Chronic mTBI/PPCS

1. Protocol:
   a. 18-65 y.o., civilian or military.
   b. Blunt or blast mTBI {ACRM definition: any LOC (< 3 0 minutes), any loss of memory before or after the accident (< 24 h), any alteration in mental state (GCS 13-15 thirty minutes post TBI), focal neurological deficits}.
   c. mTBI at least 6 months old, after 9/11/2001.
   d. Post-concussive symptoms develop in 4 weeks and be continuously present.
   e. NSI ≥ 22.

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

1. f. Headache as a symptom.
   g. DSM-IV criteria for post-concussional disorder:
      i. h/o head trauma with concussion.
      ii. Attention or memory deficits on cognitive testing.
      iii. ≥ 3/8 symptoms from shortly post concussion for ≥ 3 months: easy fatigue, disordered sleep, headache, vertigo/dizziness, irritability, anxiety/depression/affective lability, change in personality, apathy. Sx occur post concussion or are a worsening of pre-existing symptoms, causes significant impairment/decline in function, and don't meet criteria for dementia or another mental disorder.

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

1. h. Negative MAST, DAST, urine drug test, pregnancy test.
   i. Stable on current meds and no change in meds or therapies in previous 8 weeks.
   j. No cardiac arrest or shock at time of injury.
   k. Legally responsible for self.
   l. Speak/understand English.
   m. Able to sign consent forms.
   n. Otherwise good health.
   o. Long list of medical exclusions: heart, lung, neurological disease, claustrophobia, premorbid psychiatric disease, participation in an active treatment experiment, other confounding medical conditions.

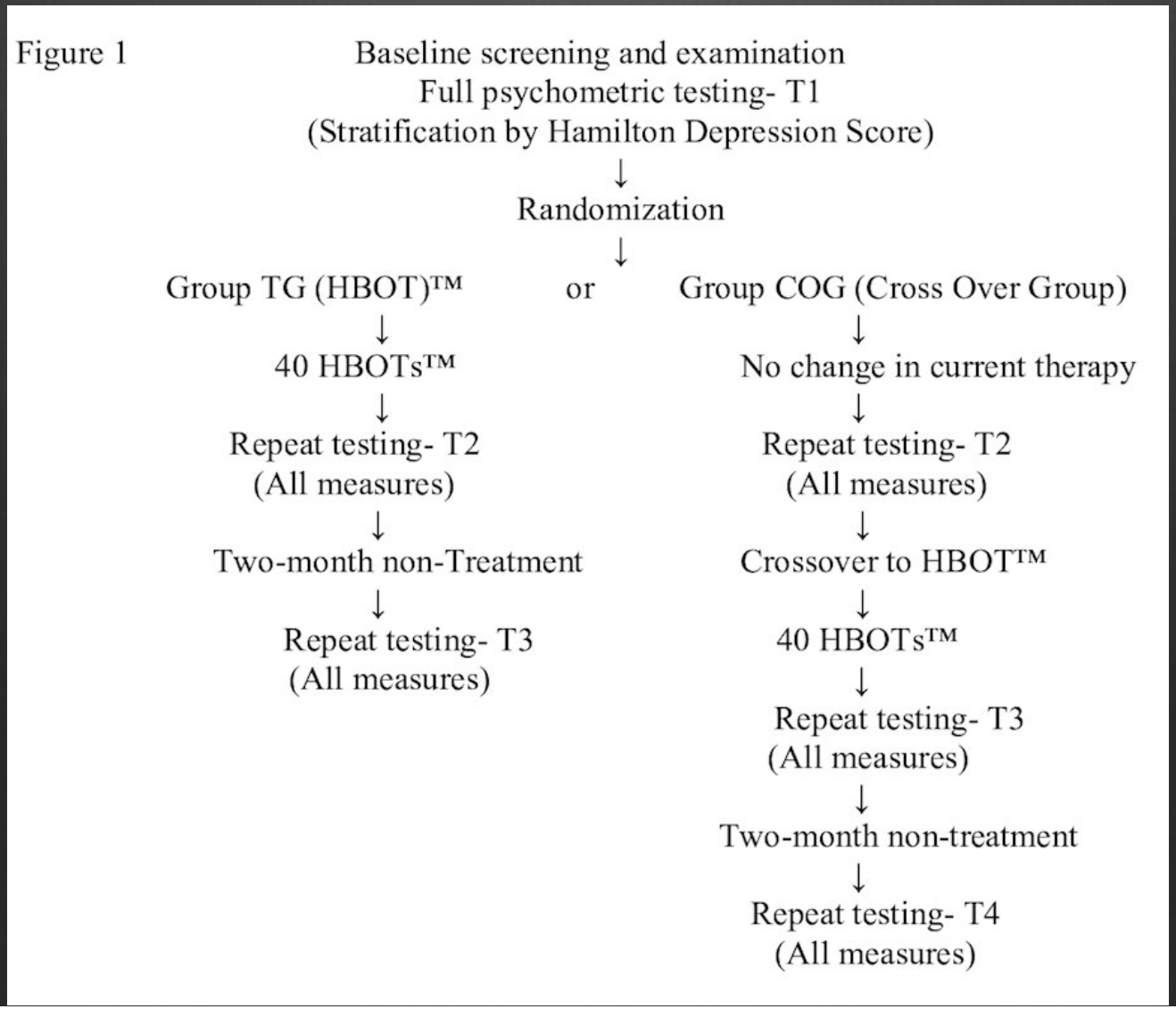
LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

2. Screening Procedure:
   a. Skype or in-person NSI, MAST, DAST, PCL, Ohio State TBI Identification Method/Interview.
   b. Clinician Administered PTSD Scale if PCL $\geq$ 50.
   c. 90 minute interview with P.I: detailed History.
   d. Travel arrangements/appointments.
   e. Enrollment
   f. Full neuropsychological test battery with effort testing (TOMM and Green Word Memory Test).
   g. 2 hour History and physical exam by the P.I., NSI, and PCL.
   h. Randomization by Hamilton Depression Score ($\geq$ 24, or < 24) to immediate treatment group (TG) or 8 week control group (COG).

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

3. Treatment
   a. HBOT, **(our original protocol)** 1.5 ATA/60 minutes total treatment time, qd, 5d/wk
      for 40 HBOTs with Vitamins C, and multivitamin.
   b. Weekly side effects symptom questionnaire and NSI.
   c. Complete retesting within one week post treatment for the TG
      and at the end of the eight week control period for the COG.
   d. Crossover of COG to HBOT for 8 weeks.
   e. Retesting of COG post HBOT.
   f. Retesting of TG and COG 8 weeks after 40th HBOT.
   g. Urine drug testing after control, treatment, and 2 mo. F/U.
   h. Pregnancy testing every 30d during HBOT.

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS



LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

4. Test Battery: addressed 3 primary deficit categories of PPCS: Sx, cognitive complaints, behavioral/ emotional changes. (6 hours long).
   a. Symptoms: measured by NSI (FDA recommendation; used by NIH, DoD, VA).
   b. Cognitive complaints: 5 category-ical variables plus Rey AVLT Delayed Recall, the ANAM 4.1, and the Benton Visual Recog. Test.

Measure	Screening	Pre-Rx	Post-Rx*	2 mos. Post Rx
New Patient Screening Checklist	X			
OSU TBI Identification Checklist	X			
NSI	X		X	X
CAPS	X			
PCL-M or C 4	X		X	X
MAST	X		X	X
DAST	X		X	X
HAMD	X		X	X
HAMA		X	X	X
TOMM	X			
WTAR	X			
Green WMT	X			
WAIS-IV		X		
WASI			X	X
WMS-IV		X	X	X
RAVLT		X		
Alternate forms			X	X
Benton VRT		X		
Alternate forms			X	X
Stroop CW		X	X	X
COWAT-FAS		X		
Alternate forms			X	X
Category Fluency		X		
Alternate forms			X	X
ANAM-4		X	X	X
PSQI		X	X	X
QOLIBRI		X	X	X

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

4. Test Battery:
   b. Cognitive complaints: 5 categorical variables:
      i. Working Memory Index: (WMS-IV Visual Working Memory Index + WAIS-IV Working Memory Index)/2.
      ii. Memory Index: (WMS-IV Immediate Memory Index + Delayed Memory Index)/2.
      iii. Executive Function Index: (t scores of Stroop Color-Word Condition +FAS Test of Verbal Fluency + Animal Test of Categorical Fluency)/3.
      iv. Information Processing Speed Index: WAIS-IV Processing Speed Index.
      v. General Intellectual Ability: WAIS-IV Full Scale IQ.

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

4. Test Battery:
   c. Behavioral/Emotional Changes: HAM-Depression Scale, HAM-Anxiety Scale, QOLIBRI (Quality of Life after Brain Injury), Pittsburgh Sleep Quality Index, PTSD Checklist.
   d. NSI and Working Memory were co-primary outcomes
   e. Alternate forms to minimize practice/test-retest effects.
   f. Testing at 3 time points for TG and 4 for the COG.
5. Statistical Analysis
   a. General linear model comparing mean differences in NSI and WM scores between TG and COG for Test 1 and Test 2.
   b. Paired samples t-tests for within group changes for all 14 tests.
   c. Chi-squared test of homogeneity for medication change and PPCS Sx change between groups Test 1-Test 2.

CONSORT Diagram:

1. 151 screened
2. 63 enrolled
3. 60 randomized:
   31 HBOT, 29 COG
4. 23 HBOT and 27 COG completed post-HBOT testing.
5. 20 HBOT and 23 COG completed two-month follow-up testing (completed study).

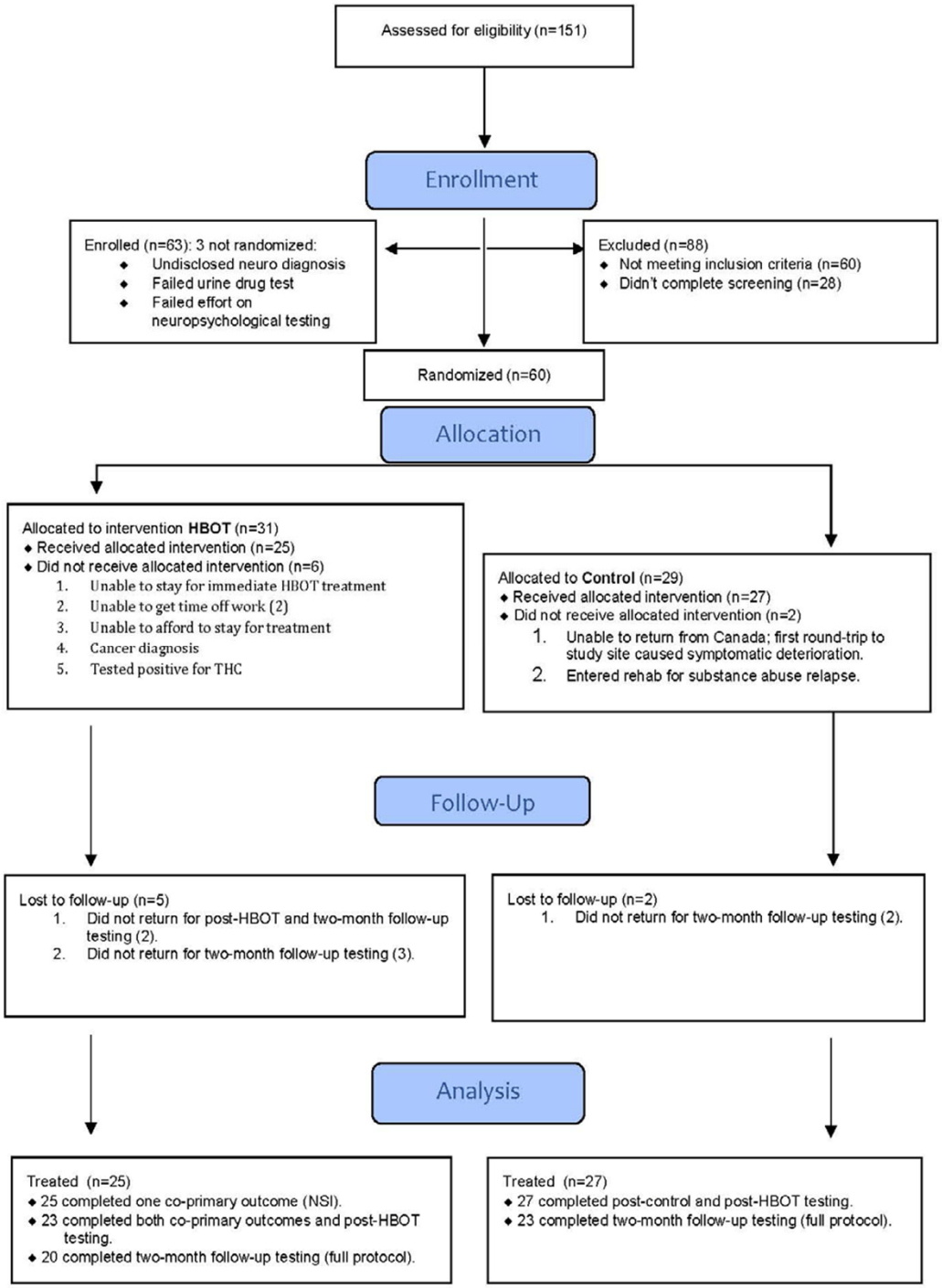


Table 1. Demographic Variables at Baseline (Test 1)

Demographic Variables	TG (23)	COG (27)	DROP (12)	p-value
Age	42.7 ± 10.7 29 (22 – 58)	42.3 ± 11.2 (22 – 60)	42.3 ± 10.8 (27 – 59)	**=0.897**
Years Education	14.0 ± 3.1 (8 – 18)	15.6 ± 1.95 (10 – 20)	15.9 ± 2.6 (13 – 20)	**=0.030***
WTAR IQ	108.7 ± 9.2 (88 – 122)	110.7 ± 6.59 (92 – 121)	114.5 ± 5.37 (100 – 122)	**=0.385**
Number TBIs In Lifetime	4.3 ± 6.2 (1 - 30)	3.6 ± 3.22 (1 – 15)	3.6 ± 3.4 (1 – 11)	**=0.646**
Time Index TBI To enrollment (d)	1598.1 ± 1099 (194.0 – 1303.0)	1748.6 ± 1471.7 (234.0 – 4460.0)	1337.9 ± 1302.3 29 (21 – 51)	**=0.695**
Time Screen To enrollment (d)	84.5 ± 71.4 (16 – 320)	60.5 ± 58.2 (17 – 305)	51.1 ± 17.7 (12 – 74)	**=0.197**
TOMM 2	49.4 ± 1.5 (45 – 50)	49.9 ± 0.77 (46 – 50)	50.0 ± 0.0 (50 – 50)	**=0.163**
Word Mem Test Consistency	92.6 ± 7.5 (77.5 – 100)	90.5 ± 10.6 (60 – 100)	90.6 ± 6.0 (80 – 100)	**=0.421**
Word Mem Test Delay Recall	95.2 ± 5.9 (80 – 100)	93.1 ± 9.4 (65 – 100)	93.5 ± 7.94 (75 – 100)	**=0.345**

Table 1. Demographic Variables at Baseline (Test 1): *Follow-up analysis: no significance among any of the 3 pairs of groups.

Word Mem Test **Immed Mem**	**94.7 ± 6.6** **(77.5 – 100)**	**92.6 ± 7.98** **(72.5 – 100)**	**93.8 ± 4.2** **(85 – 100)**	**=0.326**
Sex **% Female**	52.2% (12/23)	63% (17/27)	41.7% (5/12)	**=0.444**
Race **% Caucasian**	95.7% (22/23)	88.9% (24/27)	91.7% (11/12)	**=0.411**
Blast vs Blunt **% Blunt**	87.0% (20/23)	92.6% (25/27)	83.3% (10/12)	**=0.325**
Civil vs Military **% Military**	17.4% (4/23)	18.5% (5/27)	33.3% (4/12)	**=0.918**
Loss of Consciousness % **Yes**	73.9% (17/23)	66.7% (18/27)	83.3% (10/12)	**=0.551**
Alcohol **% Any use**	65.2% (15/23)	44.4% (12/27)	66.7% (8/12)	**=0.142**
CAPS **% Administered**	47.8% (11/23)	40.75% (11/27)	66.7% (8/12)	**=0.615**
MRI brain **% Normal**	72.7% (16/23)	59.3% (16/27)	41.7% (5/12)	**=0.318**
Tobacco **% No use**	73.9% (17/23)	77.8% (21/27)	66.7% (8/12)	**=0.750**

Table 2. Outcome Variables at Baseline (T1)

OutcomeVariables	TG (23)	COG (27)	DROP (12)	p-value TG v COG v Drop
NSI	39.0 ± 9.6 37 (24 - 58)	44.6 ± 11.8 44 (21 - 67)	34.1 ± 9.1 34 (22 – 48)	=0.029*
Working Memory	103.5 ± 12.2 103 (78 - 127)	104.6 ± 14.4 106 (79-131)	109.2 ± 10.9 106.3 (89 – 128)	=0.466
Memory	101.7 ± 14.3 100 (75 - 127)	102.9 ± 14.3 104 (72-107)	97.8 ± 11.1 95.3 (79 – 124)	=0.574
InfoProcessSpeed	94.0 ± 14.5 94 (62 - 117)	95.4 ± 15.0 97 (65-122)	98.3 ± 13.3 100 (71 – 122)	=0.709
ExecFunction	45.3 ± 8.8 44 (30 - 60)	48.1 ± 7.1 47 (37 - 64)	47.3 ± 7.9 47 (36 – 59)	=0.461
WAIS-IVFullScIQ	105.6 ± 12.3 108 (80 - 130)	106.4 ± 10.6 106 (89-128)	106.9 ± 10.3 107 (89 – 123)	=0.942
ANAM Composite Score	-1.84 ± 1.0 -1.72 (-4.2 - -0.2)	-1.6 ± 1.3 -1.3 (-3.9-0.6)	-1.11 ± 0.87 -1.2 (-2.7 – 0.2)	=0.195

Table 2. Outcome Variables at Baseline (T1) *NSI was significantly different among the 3 groups. COG and Drop groups were significantly different, but the TG and COG groups were not.

HAM-D	**15.2 ± 5.0** **16 (6 - 24)**	**14.4 ± 7.5** **15 (0 - 26)**	**15.8 ± 8.6** **15.5 (3 – 30)**	**=0.849**
HAM-A	16.5 ± 7.9 17 (2 - 35)	15.8 ± 7.3 16 (4 - 31)	17.5 ± 10.4 17 (0 – 32)	=0.835
Quality of Life	40.3 ± 12.4 40 (21 - 63)	38.9 ± 16.3 38 (8 - 85)	42.3 ± 16.9 40 (15 – 73)	=0.813
P Sleep Quality Inv	11.9 ± 4.0 12 (5 - 19)	10.5 ± 4.9 11 (2 - 20)	12.3 ± 4.8 12 (5 – 21)	=0.405
Benton Vis Mem **#Correct**	7.3 ± 1.5 8 (4 - 10)	7.0 ± 1.9 8 (3 - 10)	7.2 ± 1.5 7.5 (3 – 9)	=0.812
ReyAVLT **Delay Recall**	47.8 ± 14.0 50 (24 - 65)	47.1 ± 14.6 47 (25 - 67)	41.3 ± 9.3 42 (24 – 57)	=0.365
PTSD CheckList	37.9 ± 12.1 37 (20 – 67)	39.7 ± 13.2 37 (19 – 68)	31.6 ± 9.5 32 (19 – 48)	=0.252

Figure 3. Change in primary outcome measures and Memory Index of TG and COG during first eight-week period of the study.

	TG	COG	p value
NSI	-26.3	-2.5	<0.0001
Working Memory	+7.5	+6	=0.431

Significant reduction in symptoms
Insignificant increase in working memory

Table 3. Effect of Pre-to-Post-HBOT™ Change for TG vs Pre-to-Post Control Period for COG: Other outcomes

TG compared to Cog: significant improvement in:

Memory Index (p=0.0067)
ANAM Composite score (p=0.0069),
Ham-D **(p<0.0034)**
Ham-A **(p<0.0054)**
QOLIBRI **(p<0.0003)**
Pittsburgh Sleep Quality **(p=0.0024)**
PCL **(p>0.0001)**

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6. Results
   a. Compared to COG, TG had significant improvements in:
      i. Sx (NSI)—a co-primary outcome.
      ii. Memory Index and ANAM
      iii. Five additional variables.
      iv. Overall 12/14 variables improved in the TG vs. 5/14 in the COG.
      v. All eight PPCS definition symptoms while COG had worsening in 5/8 during the Control Period.
   b. COG improved nearly identically to TG when crossed over and received HBOT.
   c. At 2-month F/U (nearly 3 months) the two groups maintained or showed further improvement in 10/14 variables.

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6. Results
   d. By the end of the study both groups improved in 12 & 13/14 outcomes nearly identically.
   e. Both groups completed HBOT in near-identical times (57.0 vs. 56.5 days).
   f. "Two-month F/U" occurred in 79 and 80d for the two groups.
   g. 87% completed 40 HBOTs, 96% completed at least 30 HBOTs.
   h. No change in reduction in psychoactive medication use between TG and COG during first 8 weeks, but trend for TG ($p - 0.0785$).
   i. Both groups reduced psychoactive med use by 30-41%, but no difference between groups during HBOT ($p = 0.4492$).
   j. No difference NSI & PCL reduction, civilian vs. military.

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

7. Complications:
   a. 1 MEBT during an URI.
   b. 1 perforated TM in a previously perforated TM.
   c. Significant progressive fatigue with PPCS symptom exacerbation in four subjects between 30 and 39 HBOTs.
      i. Resolution in 2-4 weeks post termination of HBOT.
      ii. Interpreted as oxidative stress.
      iii. Previously reported with higher doses of HBOT and longer courses.
      iv. Reported to FDA.
      v. Modified consent.

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8. Limitations:
   a. Crossover design: precludes post-control long-term F/U. Not a major problem since natural history of PPCS is known and identified during eight week control period.
   b. Lack of blinding of subjects to allocation: Unavoidable. No acceptable pressure control. Placebo effects refuted by imaging in LSU Pilot Trial. "Ritual" refuted by Cifu DARPA study and imaging findings.
   c. Non-blinding of subjects to the P.I and NSI administration: accounts for some of the treatment effect, but does not explain all of the non-symptom improvements collected by the blinded neuropsychologist.
   d. Number of dropouts, causing increase in n of the study.

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

9. Discussion:
   a. Culmination of 30 years of investigation, including case series, animal model, case-controlled pilot trial.
   b. Re-capitulated and reinforced results and the results of others.
   c. Longest delay to treatment of any mTBI/PPCS study: 4.6 yrs.
   d. Improvement in headache ties the results to DoD study on TBI/PTSD difference, primary Sx of TBI, surrogate marker of TBI, all underscoring Rx of TBI, not just Sx.
   e. Significant results with just 50 subjects, only 23 in TG.
   f. Improvements in 3 month F/U: contrary to natural history of TBI/PPCS and uncharacteristic of placebo effects. (20-76% further improvement).

LSU RCT: IRB #7381
HBOT in Chronic mTBI/PPCS

9. Discussion:
   g. Global domain improvements c/w global imaging findings in LSU Pilot Trial and Boussi-Gross studies.
   h. Baseline memory testing for both groups that was in the "normal" range was found to not be abnormal post treatment, suggesting that the DSM-IV criteria for PPCS is erroneous.

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8. Conclusions:
   a. 40 daily, 5d/week, 1.5 ATA/60 min. HBOTs to civilian and military subjects with mTBI PPCS
      4.6 years post mTBI resulted in significant improvements in postconcussive symptoms, cognitive variables (e.g., memory, cognition/speed of information processing), and behavioral/emotional problems (anxiety, depression, PTSD symptoms, sleep, and quality of life) compared to a randomly assigned control group.
   b. These improvements were duplicated in the crossover group.
   c. In both groups improvements were sustained or improved in most domains 3 months after HBOT, suggesting HBOT as a disease-modifying therapy in mTBI PPCS.

Table 7. RPCSQ,* ImPACT,$^{\alpha}$ and NSI$^{\phi}$ outcomes, civilian and military studies of HBOT™ in mTBI/PPCS according to dose. **Original protocol 1.5 ATA O_2** dose in **bold**. Negative numbers are improvement and positive numbers are worsening of Sx.

Dose of hyper-baric therapy	No chamber treatment	1.2 ATA air	1.3 ATA air	1.5 ATA O2	2.0 ATA/ .21 ATA O2	2.0ATA/ 1.5 ATA O2	2.0 ATA O2	2.4 ATA O2
Harch 2017				**-36%***				
Wolf 2012			-32%$^{\alpha}$					-12%$^{\alpha}$
Cifu 2013					+1%*	+4%*	-12%*	
Miller 2014	-2%* +3%$^{\phi}$	-35%* -21%$^{\phi}$		**-37%*** **-11%$^{\phi}$**				
Weaver 2018		+21%* +13%$^{\phi}$		**-2%*** **-10%$^{\phi}$**				
Harch (present study)	-5.6%$^{\phi}$			**-52%$^{\phi}$**				

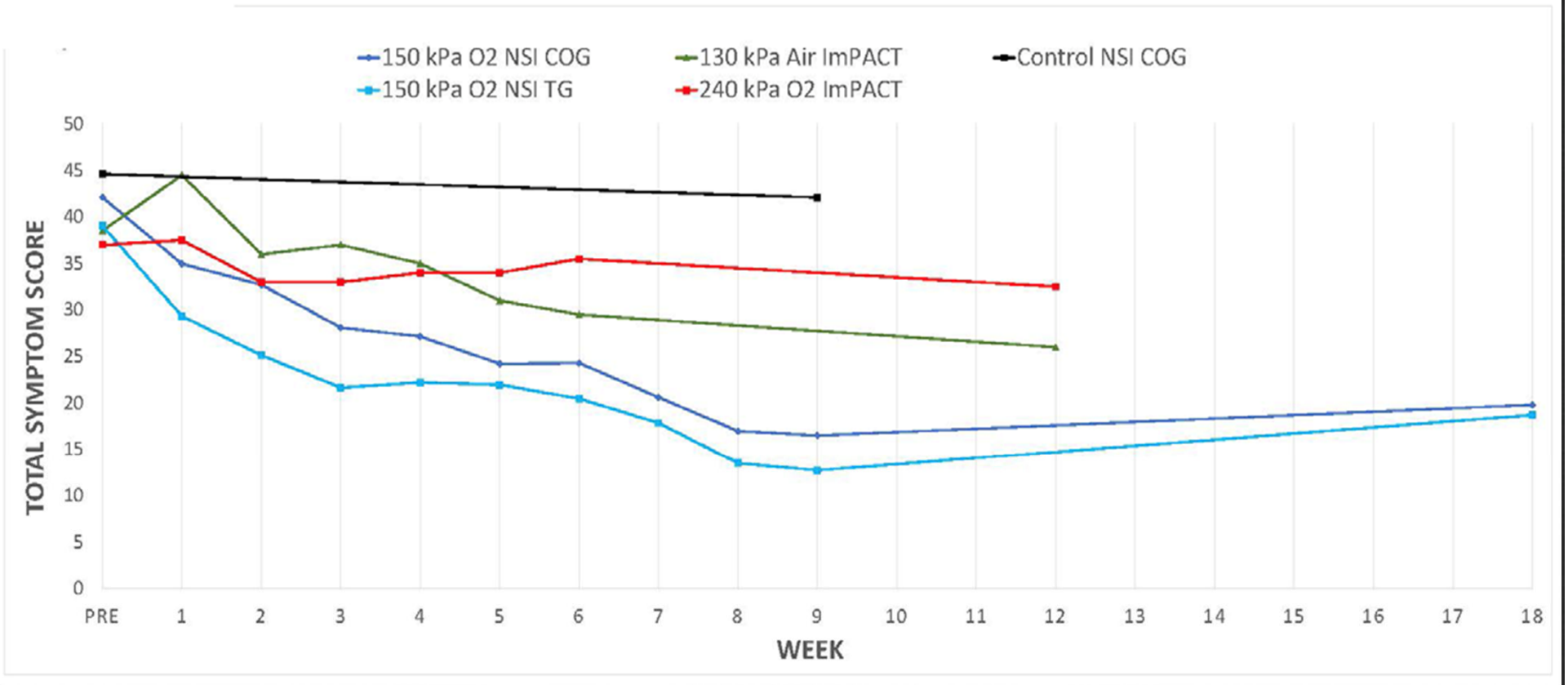
Comparison to other mTBI/PPCS studies-Durability of Improvements

1. LSU Pilot Trial: further improvement in PPCS symptoms 6 months post last HBOT.
2. Wolf, et al Trial: further improvement in PPCS symptoms 6 weeks post last HBOT.
3. Harch RCT: further improvement or maintenance of gains 3 months post last HBOT.
4. Weaver/BIMA Trial: improvements regressed at 3 and 9 months post last HBOT.
   a. Possible reasons: 70% of subjects at high risk for sleep apnea.
   b. Testing at altitude post treatment at sealevel for 2/3 sites (see Harch animal TBI study-Albuquerque).

Interpretation in terms of and reinforcement of scientific definition of HBOT. Making sense of confused science

1. HBOT is defined and understood as a dual-component drug composed of increased barometric pressure and hyperoxia that treat disease pathophysiology.
2. The differences in data and conclusions of all of the mTBI PPCS HBO studies are best explained by different effects/outcomes of different doses of hyperoxia and barometric pressure.
3. This can be seen in symptom trajectories, headache data, and symptom data.

Symptom Trajectory Data- Wolf and Harch, et al



Reduction in Headache: Comparison to other mTBI/PPCS studies

Study	1.3 ATA Air	.21 O_2/2.0 ATA Pressure	1.5 O_2/2.0 ATA Pressure	2.0 ATA O_2	1.5 ATA O_2	2.4 ATA O_2
Wolf (RPQ)	-41% p=0.002					-21% (non-significant)
Cifu (RPQ)		-9.7% p=0.23	-3.3% p=0.71	-15% p=0.12		
Harch-LSU Pilot (RPQ)					-93%	
Harch (DSM-TR PPCS Sx)					-88% p<0.0001	

Satisfying the FDA recommendation of 2011.

1. In response to a pre-IND Special Protocol Assessment in 2011, the FDA stated:
   a. We view your treatment to be composed of pressure and hyperoxia.
   b. It is unacceptable for you to investigate a single dose of HBOT, 1.5 ATA.
   c. You must do multiple studies investigating the range of pressure and oxygen doses.
2. The FDA recommendation has been met with studies at 1.2, 1.3 ATA air, 1.5 ATA oxygen, .21 ATA oxygen/2.0 ATA pressure, 1.5 ATA oxygen/2.0 ATA pressure, 2.0 ATA oxygen, and 2.4 ATA oxygen.
3. The result of all of the mTBI studies to date are:
   a. Two doses have shown benefit: 1.5 ATA oxygen, 1.3 ATA air.
   b. Three doses have shown no benefit (DARPA study).
   c. One dose has shown equivocal results (1.2 ATA air).
   d. One dose showed a trend toward harm (2.4 ATA oxygen)

American Heart Association Evidence-Based Scoring System

Classification of Recommendations

- **Class I:** Conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective.
- **Class II:** Conditions for which there is conflicting evidence, a divergence of opinion, or both about the usefulness/efficacy of a procedure or treatment.
- **Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.
- **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** Conditions for which there is evidence, general agreement, or both that the procedure/treatment is not useful/effective and in some cases may be harmful.

American Heart Association Evidence-Based Scoring System

Level of Evidence

- **Level of Evidence A:** Data derived from multiple randomized clinical trials

- **Level of Evidence B:** Data derived from a single randomized trial or nonrandomized studies

- **Level of Evidence C:** Consensus opinion of experts

Circulation 2006 114: 1761 – 1791.

Conclusion and recommendation for government and insurance companies

1. 30 years of animal and human investigation have demonstrated improvement of mTBI PPCS with hyperbaric therapy.
2. All studies at 1.5 ATA have demonstrated improvement in symptoms and cognition. One study at 1.3 air demonstrated improvement in symptoms.
3. The collection of studies at 1.5 ATA HBOT to date meets American Heart Association Class I Level A Evidence-based medicine criteria to strongly argue for government and insurance reimbursement of HBOT for this diagnosis.

Conclusion and recommendation for government and insurance companies

However, as demonstrated by oxidative stress/overdosing treatment and dosing should be individualizerd to patient response.

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Conclusions

- mTBI is primarily a white matter injury, resulting in white matter wounds.
- Inflammation is a significant component of chronic TBI wounds.
- HBOT is a treatment consisting of increased pressure and increased oxygen whose effects are dependent on dose.
- HBOT is a treatment of wounds with significant gene modulatory effects and effects on inflammation.
- A review of the literature on HBOT in mTBI/PPCS with or w/o PTSD shows varying effects of different doses of HBOT.
- 1.5 ATA HBOT meets AHA criteria for Evidence-Based Medicine treatment of mTBI/PPCS and should be reimbursed.

Thank You