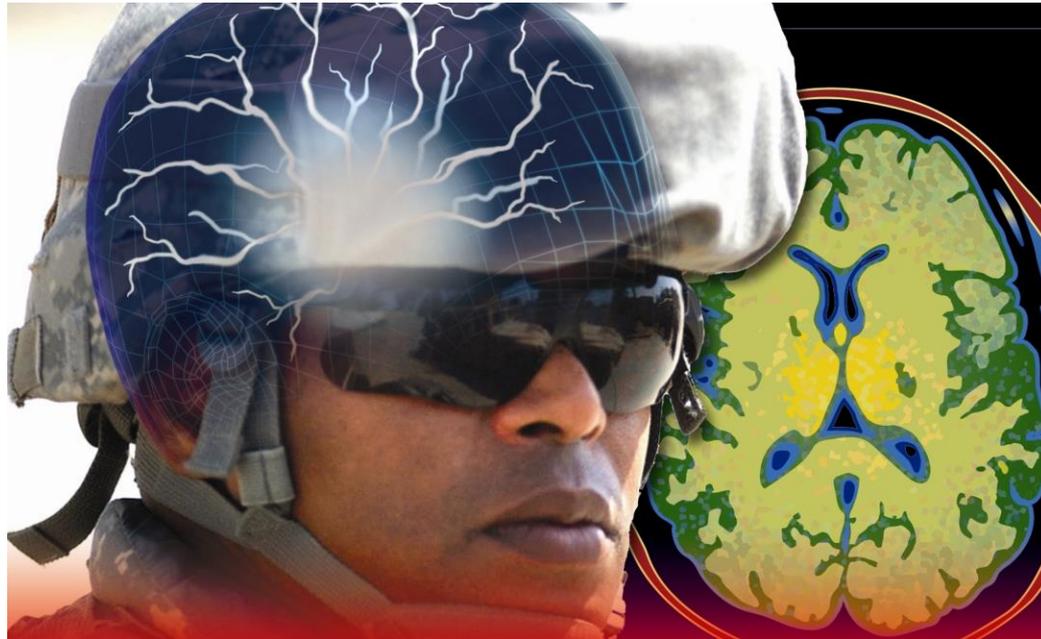


The Use of HBO for Persistent Symptoms after mTBI



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Disclosure

The views expressed in this presentation are those of the author and do not reflect official policy or position of the Department of Veteran Affairs or the U.S. Government.

Topic Outline

- Examining Theory – A Role for HBO in Persistent Symptoms after mild TBI
- Clinical Trials of HBO in Persistent Symptoms after mild TBI

Poll Question #1

- Which best describes your research experience?
 - have not done research
 - have collaborated on research
 - have conducted research myself
 - have applied for research funding
 - have led a funded research grant

Poll Question #2

- Which best describes your TBI research experience?
 - have not done research
 - have collaborated on research
 - have conducted research myself
 - have applied for research funding
 - have led a funded research grant

The Impact of TBI

Mechanisms of Injury - Sports



The Impact of TBI

Mechanisms of Injury - MVAs



The Impact of TBI

Mechanisms of Injury - Others



The Impact of TBI

Mechanisms of Injury - Military

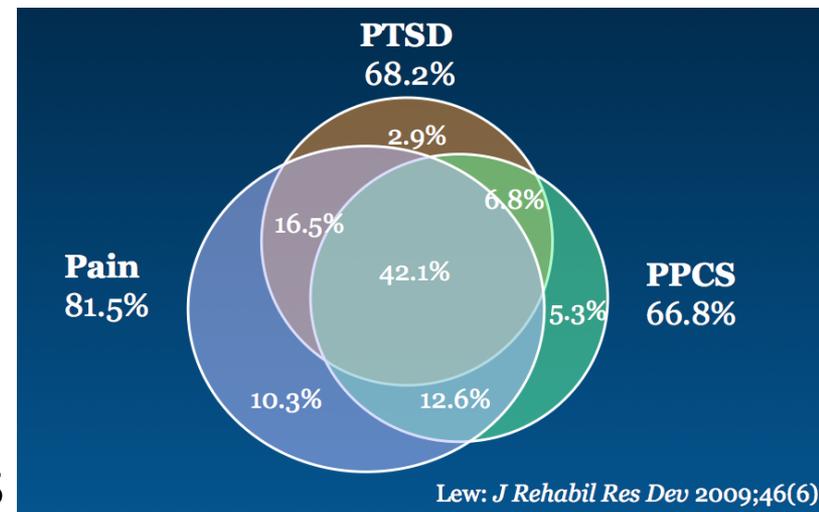


Persistent Symptoms after mTBI

- ↗ Dizziness
- ↗ Loss of Balance
- ↗ Poor coordination
- ↗ Headaches
- ↗ Nausea
- ↗ Visual disturbance
- ↗ Light sensitivity
- ↗ Hearing difficulty
- ↗ Noise sensitivity
- ↗ Body/extremity numbness
- ↗ Altered taste or smell
- ↗ Appetite change
- ↗ Poor concentration
- ↗ Forgetfulness
- ↗ Difficulty making decisions
- ↗ Slowed thinking
- ↗ Fatigue
- ↗ Insomnia
- ↗ Feeling anxious
- ↗ Feeling depressed
- ↗ Easily irritated
- ↗ Poor frustration tolerance

Overlap of Symptoms Complexes

- No Symptom Unique/Diagnostic for mTBI
- “Post-Concussive” Symptoms Present in “Normals”
- Symptoms Overlap with:
 - PTSD
 - Chronic Pain
 - Depression / Anxiety
 - Somatoform Disorders
 - Chronic Health Conditions



**Persistent Symptoms after
TBI Pathophysiology –
The Cell's Perspective**

TBI Pathophysiology

The Cell's Perspective

- Primary Insult Effects
 - Direct Mechanical Damage at Time of Insult
 - Respond to Preventive Measures
- Secondary Insult Effects
 - Delayed Non-Mechanical Effects
 - Respond to Treatment Measures

TBI Pathophysiology

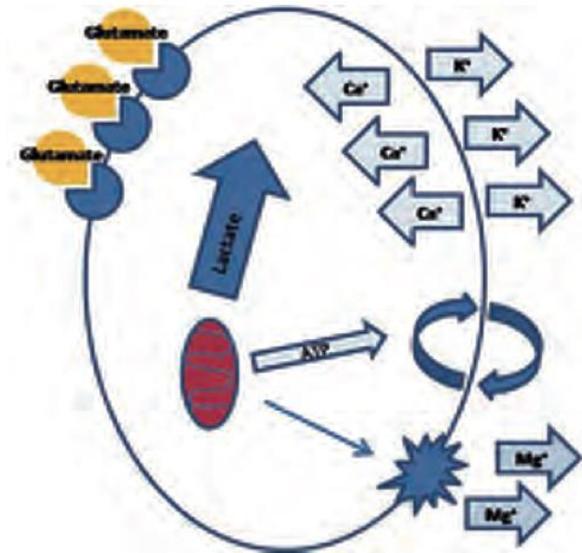
The Cell's Perspective

- Initial Stages of Injury
 - Direct Tissue Trauma
 - Impaired Blood Flow
 - CO₂ Responsiveness
 - Vasospasticity
 - Hyper / Hypoperfusion
 - Impaired Regulation Metabolism
 - Increased Cellular Work
 - Glucose / Lactate Imbalance

TBI Pathophysiology

The Cell's Perspective

- Secondary Stages of Injury
 - Cellular Ischemia
 - Anaerobic Metabolism
 - \uparrow Membrane Permeability
 - Edema Formation
 - Excitatory Neurotransmitters
 - Glutamate, Aspartate Release
 - Activation of NMDA / Ca^{++} / Na^+ Channels



TBI Pathophysiology

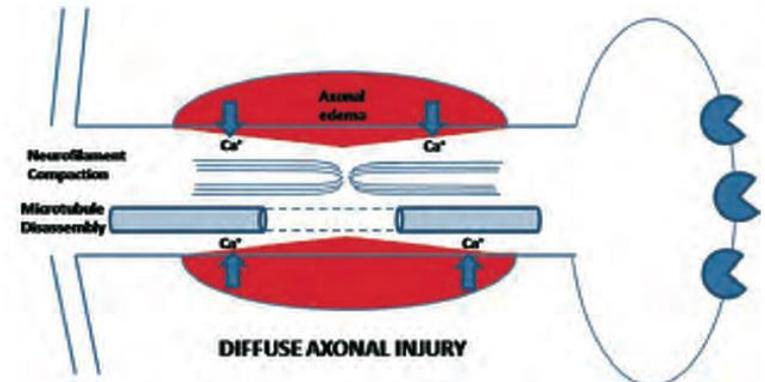
The Cell's Perspective

- Secondary Stages of Injury
 - Catabolic Intracellular Processes
 - Lipid Peroxidase, Protease, Phospholipase Activation
 - Free Radical & Free Fatty Acid Accumulation
 - Caspase & Calpain Mediated Cleavage
 - Cellular Apoptosis

TBI Pathophysiology

The Cell's Perspective

- Cellular Level Injury
 - Cellular Metabolism
 - Intracellular Transport
 - Cellular Transmission
 - “Diffuse Axonal Injury”
 - Intracellular / Intercellular Communication
 - Intercellular Metabolic Transport
 - Both Neurons and Glial Cells Affected



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**Examining Theory –
A Role for HBO in Persistent
Symptoms after mTBI**

Examining Theory

A Role for HBO in mTBI

Snake Oil



Science?





Examining Theory

“Accepted” HBO Clinical Indications

	UHMS Accepted Indications	CMS Accepted Indications
1	Air or Gas Embolism	Gas Embolism
2	Decompression Sickness	Decompression Illness
3	Carbon Monoxide (± CN) Poisoning	Carbon Monoxide (± CN) Poisoning
4	Exceptional Blood Loss (Anemia)	N/A
5	Crush Injury, Compartment Syndrome, Other Acute Traumatic Ischemia	Crush Injury & suturing severed limbs, Acute Traumatic Peripheral Ischemia, Acute Peripheral Arterial Insufficiency
6	Skin Grafts & Flaps (Compromised)	Preparation & Preservation of Compromised Skin Grafts (not primary)
7	Thermal Burns	N/A
8	Delayed Radiation Injury (Soft Tissue and Bony Necrosis)	Osteoradionecrosis and Soft Tissue Radionecrosis
9	Enhancement of Healing in Selected Problem Wounds	Diabetic Wounds of the Lower Extremity (with restrictions)
10	Clostridal Myositis and Myonecrosis (Gas Gangrene)	Gas Gangrene
11	Necrotizing Soft Tissue Infections	Progressive Necrotizing Infections
12	Osteomyelitis (Refractory)	Chronic Refractory Osteomyelitis
13	Intracranial Abscess	Actinomycoses



Examining Theory

Six Basic HBO Mechanisms

- 1) Diffusion and Mechanical Compression
- 2) Antibacterial Response Modulation
- 3) Correction of Cellular Hypoxia
- 4) Peripheral Vasoconstriction
- 5) Reperfusion Injury Modulation
- 6) Stimulation of Cellular Repair

Examining Theory

Potential HBO Applications to TBI

HBO ₂ Mechanism	Acute TBI	Chronic TBI
Diffusion and Mechanical Compression	Not Applicable	Not Applicable
Modulation of Antibacterial Response	Not Applicable	Not Applicable
Correction of Cellular Hypoxia	Likely	Possible
Vasoconstriction	Likely	Unlikely
Reperfusion Injury Prophylaxis	Possible	Unlikely
Stimulation of Cellular Repair	Possible	Possible

Examining Theory

Proposed HBO Effects on TBI

- Reduction of Cerebral Edema
- Enhance Oxygen Availability to Revive “Penumbra” Neurons
- Influence Neurotransmitter Function / Availability (nitric oxide mediation)
- Immune Modulation
- Stem Cell Mobilization to Sites of Injury

Examining Theory

Proposed HBO Effects on TBI

- Bottom Line – Basic Science Still Lacking!



HBO for TBI Management

Clinical Trials

HBO Animal Research in TBI

- Systemic Review of Animal (Rodent, Cat, Dog) Research Supports HBO use in acute moderate to severe TBI
 - Reduces Acute Cerebral Edema
 - Reduces Markers of Cerebral Inflammation
 - Increases Cerebral Perfusion
 - Enhances Spatial Learning / Task Following
- Also in Chronic Moderate-Severe TBI

HBO in Animal TBI Research

- Animal Literature Caveats
 - HBO₂ Treatment Initiation
 - Animals Usually Minutes to ~ 2 Hours Post Injury
 - Humans Usually 6+ Hours to Days Post Injury
 - No HBO₂ Research in mTBI
 - No Direct Translation to Human Outcome

HBO in Human TBI Research

– Human Studies

- Four Systematic Reviews of moderate-severe TBI
 - Included 23 publications (1972-2001)
 - Only four studies (382 subjects, 199 HBO₂ & 183 controls) met review criteria for scientific evaluation
 - Assessed acute, traumatic, moderate/severe TBI
 - Concluded current scientific evidence insufficient to prove effectiveness / ineffectiveness of HBO for TBI
- 6 Clinical Trials Published in mTBI

HBO in Human TBI Research

- Overall Study Quality Assessed as Low*
- No Sham Therapy Included
- Randomization Inadequate*
- Blinding Not Used**
- Non-Standard Inclusion Criteria Across Trials

* Except Rockswold '10 Trial

** Except Rockswold '92 Trial

HBO in Human TBI Research

- Non-significant trend ($P \leq 0.08$) Favorable Outcome of full recovery or return to ADL 1.5 years post-injury
- Three trials showed a significant reduction (RR 0.69, 95%CI 0.54-0.88) in risk of dying (mortality) with ‘numbers needed to treat’ being 7
- No reduction in coma persistence or duration
- Effects on ICP and Pulmonary Status Only assessable secondary outcome measures

HBO in Human TBI Research

- Incidence of adverse events reported among 186 patients in 4 studies – 11.3%
 - Three Seizures – 1.6%
 - Fifteen Pulmonary Symptoms – 8%
 - Two Otic Barotraumas – 1.1%

HBO in Human TBI Research

- No scientifically rigorous research has been published in acute mild TBI or moderate TBI or chronic TBI of any severity (until last decade)

HBO in Human TBI Research

Clinical Trials of HBO for Persistent Symptoms after mTBI

Clinical Trials

US Air Force Trial (17DEC2008) – Completed		
Study Name	Treatment of Moderate to Mild Cognitive Dysfunction Caused by Traumatic Brain Injury (TBI) with Hyperbaric Oxygen Therapy (HBOT)	
PIs	Col Robert Michaelson, Maj Gerald York, Col (ret) George Wolf	
Sites	San Antonio Military Medical Center, San Antonio, Tx	
Inclusion Criteria	19-60 years old, mild – moderate TBI, researcher confirmed diagnosis, stable status and medications	
Study Design	Randomized, Prospective, Sham Controlled, Single Blind	N = 50
Study Tests	ImPACT, ANAM, TOVA, PCL-M, fMRI, Biomarkers	
Protocol Groups	Sham – 1.3 ATA Air (3 x 30 min, w / 10 min air breaks), 30 Exposures HBO2 – 2.4 ATA Oxygen (3 x 30 min, w / 10 min air breaks), 30 Exp	
Findings	No b/n group differences of mTBI or PTSD sx's or cognition. Improvements seen in both groups. 5% incidence minor AEs	
Reference	Wolf: J Neurotrauma 2012;29	Wolf: UHM 2012;39(6)

Clinical Trials

Intermountain Health Care, Inc. (27JAN2009) – Completed	
Study Name	Hyperbaric Oxygen Therapy in Chronic Stable Brain Injury (HYBOBI)
PIs	Dr. Lin Weaver & Susan Churchill, APRN-NP
Sites	LDS Hospital, Salt Lake City, Utah
Inclusion Criteria	18-80 years old, chronic, stable, mild brain injury sequelae (secondary to stroke, anoxia or trauma), confirmed by questionnaires / testing
Study Design	Observational, Prospective, Unblinded, Self-Control Cohort N = 63
Study Tests	Neuropsychological testing, functional measures, health-related quality of life measures, and neurological examination, subjects own controls.
Protocol Groups	All subjects receive intervention (1.5 ATA oxygen, 60 minutes), 60 total sessions
Results	No clinically meaningful improvements noted, however statistical improvements in symptoms reported in >50%, and >90% would like to participate in further HBOT trials.
Reference	Churchill: UHM 2013;40(2)

Clinical Trials

International Hyperbaric Medical Foundation (15APR2010) – Completed	
Study Name	Multicenter Observational Trial Hyperbaric Oxygen Therapy in Chronic Traumatic Brain Injury or Post-Traumatic Stress Disorder (NBIRR-1)
PIs	Dr. James Wright & Dr. Paul Harch
Sites	Multiple sites: currently 14 active, but number not specifically limited
Inclusion Criteria	18-65 years old, mild – moderate TBI <u>or PTSD</u> , diagnosis by any prior evaluation, 20% performance decrement on ANAM / “reaction time”
Study Design	Observational, Prospective, Unblinded, Self Control Cohort N = 16
Study Tests	Computerized neurocognitive, SPECT, QoL
Protocol Groups	All subjects receive intervention (1.5 ATA oxygen, 60 minutes), Plan 40 sessions, but extend “as indicated” to 60 – 80 sessions
Results	Improvements noted in Sx’s, cognition, QoL and SPECT scans
Reference	Harch: J Neurotrauma 2012;29(1)

Clinical Trials

VCU - VA - US Navy Trial (06OCT2010) – Completed	
Study Name	Hyperbaric Oxygen Therapy (HBO2T) for Post-Concussive Symptoms (PSC) After Mild Traumatic Brain Injury (mTBI)
PIs	Dr. David Cifu, CAPT Brett Hart, Michelle Nichols BSRN
Sites	Hunter Holmes McGuire VA Medical Center, Richmond, VA – Testing Naval Operational Medicine Institute, Pensacola, FL – HBO ₂ Exposure
Inclusion Criteria	19-60 years old, chronic, stable, mTBI, researcher confirmed by questionnaires / testing
Study Design	Randomized, Prospective, Double Blind, Sham Controlled N = 60/20
Study Tests	9 Symptom Assess, 12 Neuropsych, Computerized Posture, Eye Track
Protocol Groups	Group A: 2.0 ATA (100% O ₂ - 2.0 ATA Equivalent), 40 Sessions, 60 min Group B: 2.0 ATA (75% O ₂ - 1.5 ATA Equivalent), 40 Sessions, 60 min Group C: 2.0 ATA (10.5% O ₂ - 1.0 ATA Equivalent), 40 Sessions, 60 min
Results	No b/n group differences of mTBI or PTSD sx's or cognition. Improvements seen in both groups. 1% incidence minor AEs

Clinical Trials

Cifu Study References:

- Cifu DX, Hoke KW, Wetzel PA, Wares JR, Gitchel G, Carne W. Effects of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. 2014.
- Walker WC, Franke LM, Cifu DX, Hart BB. Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention. *Neurorehabil. Neural Repair* 2013;28(5):1545968313516869-. doi:10.1177/1545968313516869.
- Cifu DX, Hart BB, West SL, Walker W, Carne W. The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms. *J. Head Trauma Rehabil.* 2014;29(1):11-20. doi:10.1097/HTR.0b013e3182a6aaf0.
- Cifu DX, Walker WC, West SL, et al. Hyperbaric oxygen for blast-related postconcussion syndrome: Three-month outcomes. *Ann. Neurol.* 2014;75(2):277-286. doi:10.1002/ana.24067.

Clinical Trials

Israeli mTBI Study– Completed	
Study Name	Hyperbaric Oxygen for Symptoms after mild TBI
PIs	R. BoussiGross and H Golan (University of Tel Aviv)
Sites	Tertiary Care Hospital, Tel Aviv, Israel
Inclusion Criteria	18-65 years old, Mild TBI exposure with persistent symptoms
Study Design	Randomized, Prospective, Cross Over Study N = 56
Study Tests	Computerized Neurocognitive, QoL, SPECT
Protocol Groups	Group 1 HBOT 1.5 ATA/60 min/40 sessions then no HBOT 2 mos Group 2 No HBOT 2 mos then HBOT 1.5 ATA/60 min/40 sessions
Results	No improvements during no HBOT/Crossover, but improvements in cognition, QoL and SPECT
Reference	Boussi-Grioss: PLoS One 2013;8(11)

Clinical Trials

US Army MRMC Trial (24FEB2011) – Completed		
Study Name	A Pilot Phase II Study of Hyperbaric Oxygen for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (HOPPS)	
PIs	Col Scott Miller, Dr. Lin Weaver, Susan Churchill APRN NP	
Sites	Naval Hospital Camp Pendleton, CA; Evans Army Hospital , Ft.Carson, CO; Eisenhower Army Med. Center, Fort Gordon, GA	
Inclusion Criteria	18-65 years old, Cohort 1 – PTSD, Cohort 2 – chronic, stable, mTBI , researcher confirmed by questionnaires / testing	
Study Design	Randomized, Prospective, \pm Single Blind, Sham Controlled	N = 72
Study Tests	RPQ, NSI, 19 Others Secondary, Dynavision, 6-Minute Walk Test	
Protocol Groups	Cohort 1 and 2(a): PTSD or (b) mTBI, No Intervention, Local Care Cohort 2(c): mTBI, Active (1.5 ATA Oxygen, 60 min), 40 Sessions Cohort 2(d): mTBI, Sham Control (1.2 ATA Air, 60 min), 40 Sessions	
Results	No b/n group differences of mTBI or PTSD sx's or cognition. Improvements seen in both groups. 1% incidence minor AE's.	
Reference	Miller: JAMA Intern 2015;175(1)	

**HBO for Persistent
Symptoms after mTBI –
What Now?**

Management of Persistent Symptoms of

- Multi-Modal Etiology
- Mechanism of Injury and Symptoms
- Site of Injury and Symptoms
- Severity of Injury and Symptoms
- Chronicity of Symptoms
- Subject Characteristics

...Treat using standardized protocol !

Conclusions

- Mild TBI is a common Injury in civilian and military arenas
- Persistent Post-Concussive Symptoms are common
- Identifying Etiologies may be important, but is rarely conclusive.
- HBOT is NOT a recommended intervention for persistent symptoms after mTBI (or PTSD).

HBO for Persistent Symptoms following mTBI

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Questions?