Controversies in the Use of HBO₂ for Symptomatic mTBI

David X. Cifu, MD
National Director, PM&R Services
Department of Veterans Affairs

Chairman and Herman HJ. Flax, M.D. Professor
Department of Physical Medicine and Rehabilitation
Virginia Commonwealth University

DCIFU@VCU.EDU
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.
Why is DoD/VA studying HBOT for TBI?

Examining Theory – A Role for HBO$_2$ after TBI?

Applying HBO$_2$ to PCS – Trials & Tribulations
Why is DoD/VA studying HBOT for TBI?
Why is DoD/VA studying HBOT for TBI?

- Increasing incidence of TBI in Military and Veteran populations.
- Persistence of symptomatic mTBI after combat-related injuries.
- Pressures from VSO, Lobbyists, constituents.
- Pressures from Congress and DoD leadership.
Why is DoD/VA studying HBOT for TBI?

- Increasing incidence of TBI in Military and Veteran populations.
Civilian TBI experience

- Most common cause of disability / death young people
- 1.5 million TBIs annually
- TBI disability in 2% US population; 50,000 deaths
- 80% mild, 10% moderate, 10% severe
- $56.3 billion/yr

CDC, 2006
The Impact of TBI
Mechanisms of Injury – Military Combat
The Impact of TBI
Mechanisms of Injury – Military non-Combat
The Impact of TBI

TBI in U.S. Military 2000-2012

- Severe: 2,124
- Moderate: 34,001
- Mild: 155,623
- Total: 223,000

(2000 - FEB 2012)
Iraq/Afghan Wars and TBI

- 15-23% of all deployed SMs have TBI or ~350,000\(^1\)
  > 233,000 confirmed by DoD\(^2\)
  ~ 2,500 mod/severe

- 6.7% of all OEF/OIF SMs who have come to VA (750,000 or 55% of those eligible) have symptomatic mTBI\(^3\)

- 73% of Vets with symptomatic mTBI also have mental health diagnosis (usually PTSD)\(^3\)

\(^1\) Congressional Budget Office
\(^2\) www.dvbic.org/tbi-numbers.aspx
\(^3\) www.queri.research.va.gov/ptbri/docs/vha-tbi-screening-eval.pdf
Costs of OEF/OIF TBI care in VA for FY2011

- PTSD alone = $8,300
- TBI alone = $11,700*
- TBI + PTSD = $13,800*
- Neither = $2,400

* excludes all inpatient rehabilitation costs

Total = $2 billion of overall care

Source: Congressional Budget Office
Why is DoD/VA studying HBOT for TBI?

- Persistence of symptomatic mTBI after combat-related injuries.
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}

*Cicerone: J Head Tr Rehabil 1995;10(3):1-17*
The Impact of TBI
Symptom Characteristics

Immediate

Day 3

Day 7

85% of subjects full symptom recovery within 1 week

Persistent Symptoms after mTBI

Why is the incidence of persistent symptoms 2-3x higher than civilians and why are there so many more symptoms?
Is it simply Post-Concussive Syndrome?

- PCS = Non-Focal, Neurologic Symptoms Remain One\(^1\) to Three\(^2\) Months after TBI

- “Persistent” Post-Concussive Symptoms in Military
  - Irritability 21%
  - Headache 20%
  - Memory 16%
  - Imbalance 6%
  - Dizziness 5%

\(^1\)WHO-ICD-10; 1992; \(^2\)DSM-IV; 1994
The Impact of TBI
Blast Injury Multimodal

Wall of Air (Primary)
Blast Wind (Primary)
Flying Debris (Secondary)
Displacement (Tertiary)
Collapse Building (Quaternary)
Epidemiology: Overlap of PDS

PTSD: 68.2%

Pain: 81.5%

PPCS: 66.8%

Lew: J Rehabil Res Dev 2009;46(6)
Post-Deployment Syndrome

- 15-20% OEF-OIF Service Members and 6.7% of Veterans are returning with persistent physical and psychological symptoms after combat exposure.

- Controversies concerning etiology of symptoms
  - Blast exposure
  - Post-concussive syndrome
  - Post-traumatic stress disorder
  - Depression
  - P3+ (PTSD, Polytrauma, PTSD, Polysubstance Use, Pain)
  - Environmental factors
  - Impact of multiple exposures (blast, trauma)
PDS: A Complex Condition

Mild TBI

Depression

Post Deployment Syndrome

Blast

Combat-related Stress

Substance Use

Pain

Environment

Systemic Factors
Why is DoD/VA studying HBOT for TBI?

- Pressures from VSO, Lobbyists, constituents.
Belief that current TBI “treatments” are non-proven and non-scientific.

Concern for long-term effects of mTBI
- Less an issue of disabling impact of symptoms
- Strong focus on Chronic Traumatic Encephalopathy

Anecdotal reports of efficacy with HBOT.

Financial rewards.

Testimonials from patients.
Does TBI exposure lead to degenerative encephalopathy?

- The effects of TBI on later-life are poorly understood, particularly in (mTBI)
- Recent studies suggest that even mTBI leads to an increased risk of later-life cognitive impairment and neurodegenerative disease, especially when repeated injuries are involved. Gavett 2011; Guskiewicz 2005
- TBIs of mixed severity have been associated with an elevated incidence of Alzheimer’s disease (AD) and other dementias\(^1\)\(^-\)\(^3\) and a reduced age of onset for AD,\(^4\) although not in all studies.\(^5\)

\(^1\)\(^-\)\(^3\)Plassman 2000; Bower 2003; Mortimer 2010
\(^4\)Nemetz 1999
\(^5\)Williams 1991
Does mild TBI exposure lead to degenerative encephalopathy?

- Previously, CTE had been almost exclusively studied in boxing, wherein retired boxers developed dementia at a higher rate and a younger age compared to the general population.  
  
  McKee 2009  
  Corsellis 1973

- Microscopically, there are extensive tau-immunoreactive neurofibrillary tangles, astrocytic tangles, and spindle-shaped and threadlike neurites throughout the brain. CTE is a neuropathologically distinct, slowly progressive tauopathy with a clear environmental etiology.  
  
  McKee 2009
Why is DoD/VA studying HBOT for TBI?

- Pressures from Congress and DoD leadership
Political Pressures for mTBI Treatments

- Concern for troop readiness.
- Concern for troop recruitment.
- High profile of Congresswoman Gifford.
- DoD and VA need to lead the way.
Controversies in the Use of HBO₂

PCS 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
PCS 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
Secondary Stages of Injury

- Cellular Ischemia
  - Anaerobic Metabolism
  - ↑ Membrane Permeability
  - Edema Formation

- Excitatory Neurotransmitters
  - Glutamate, Aspartate Release
  - Activation of NMDA / Ca\(^{++}\) / Na\(^+\) Channels
Secondary Stages of Injury

Catabolic Intracellular Processes
- Lipid Peroxidase, Protease, Phospholipase Activation
- Free Radical & Free Fatty Acid Accumulation
- Caspase & Calpain Mediated Cleavage

Cellular Apoptosis
Controversies in the Use of HBO$_2$

Examining Theory –
A Role for HBO$_2$ in
PCS/PDS?
Examinining Theory
A Role for HBO₂ in PCS?

Snake Oil

Science?

Politics or…
# Examining Theory

## Potential HBO₂ Applications to TBI

<table>
<thead>
<tr>
<th>HBO₂ Mechanism</th>
<th>Acute TBI</th>
<th>Chronic TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion and Mechanical Compression</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Modulation of Antibacterial Response</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Correction of Cellular Hypoxia</td>
<td>Likely</td>
<td>Possible</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Likely</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Reperfusion Injury Prophylaxis</td>
<td>Possible</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Stimulation of Cellular Repair</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Examining Theory
Proposed HBO\textsubscript{2} 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$_2$ Effects on TBI

Bottom Line – Basic Science Still Lacking!
Controversies in the Use of HBO$_2$

Applying HBO$_2$ to PCS – Trials and Tribulations
Controversies in the Use of HBO₂
Talking to the Animals

- Systemic review of animal (rodent, cat, dog) research supports HBO₂ use in acute TBI
- Acutely, HBO₂ significantly
  - Reduces acute cerebral edema
  - Reduces markers of cerebral inflammation
  - Increases cerebral perfusion
  - Enhances spatial learning / task
- Shown also to enhance cognitive outcomes in chronic moderate-severe TBI
Caveats in examining animal literature

HBO\textsubscript{2} treatment initiation
- Animals usually begun minutes to 2 hours post injury
- Humans usually 6+ hours to days post-injury

No HBO\textsubscript{2} research in mTBI (acute or chronic)
mTBI animal model lacking and PCS hard to understand in animal
No direct translation of animal TBI work to humans
Human Studies

Four Systematic Reviews

- 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 HBO₂ for TBI

Two reviews and two trials published since 2001.
Controversies in the Use of HBO$_2$
The Human Research Experience

- Summary of acute human usage (in severe TBI):
  - One trial showed trend ($P \leq 0.08$) towards favorable outcome at 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.
  - Enhanced mortality seem to be related to effects on ICP and pulmonary status.
Controversies in the Use of HBO₂
The Human Research Experience

- Summary of adverse events (186 patients in 4 studies) = 11.3%
  - Three Seizures – 1.6%
  - Fifteen Pulmonary Symptoms – 8%
  - Two Otic Barotraumas – 1.1%
Controversies in the Use of HBO$_2$

The Human Research Experience

- Caveats of Human Literature:
  - Overall study quality assessed as low
  - No sham therapy included
  - Randomization inadequate
  - Blinding not used
  - Non-standard inclusion criteria across trials

- No scientifically rigorous human research has been published in acute mild/moderate TBI or chronic TBI of any severity.
Controversies in the Use of HBO₂

HBO₂ for persistent symptoms after mTBI – The current DoD/VA clinical trials
There are presently 4 DoD supported HBOT trials for persistent symptoms after mTBI.
- Pilot study (HBOT vs Sham) completed
- Pilot study (outcome measure validation) completed
- Pilot study (HBOT [2 dose] vs Sham) underway – 60% completed
- Definitive trial begun January 2012

There is also 1 non-DoD open-label trial (Harch – LSU) underway
- Non-randomized
- No sham or control
# Controversies in the Use of HBO₂

## The Current Clinical Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Treatment of Moderate to Mild Cognitive Dysfunction Caused by Traumatic Brain Injury (TBI) with Hyperbaric Oxygen Therapy (HBOT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Col Robert Michaelson, Maj Gerald York, Col (ret) George Wolf</td>
</tr>
<tr>
<td>Sites</td>
<td>San Antonio Military Medical Center, San Antonio, Tx</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>19-60 years old, mild – moderate TBI, researcher confirmed diagnosis, stable status and medications</td>
</tr>
<tr>
<td>Study Design</td>
<td>Randomized, Prospective, Sham Controlled, Single Blind [N = 50]</td>
</tr>
<tr>
<td>Study Tests</td>
<td>ImPACT, ANAM, TOVA, PCL-M, fMRI, Biomarkers</td>
</tr>
<tr>
<td>Protocol Groups</td>
<td>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.</td>
</tr>
</tbody>
</table>
## Controversies in the Use of HBO₂

### The Current Clinical Trials

<table>
<thead>
<tr>
<th>Intermountain Health Care, Inc. (27JAN2009) – Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Name</strong></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
</tr>
<tr>
<td><strong>Sites</strong></td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
</tr>
<tr>
<td><strong>Study Tests</strong></td>
</tr>
<tr>
<td><strong>Protocol Groups</strong></td>
</tr>
</tbody>
</table>
### VCU - VA - US Navy Trial (06OCT2010) – Active / Recruiting

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Hyperbaric Oxygen Therapy (HBO2T) for Post-Concussive Symptoms (PSC) After Mild Traumatic Brain Injury (mTBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Dr. David Cifu, CAPT Brett Hart, Dr. William Walker</td>
</tr>
<tr>
<td>Sites</td>
<td>Hunter Holmes McGuire VA Medical Center, Richmond, VA – Testing Naval Operational Medicine Medicine Institute, Pensacola, FL – HBO₂ Exposure</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>19-60 years old, chronic, stable, mTBI, researcher confirmed by questionnaires / testing</td>
</tr>
<tr>
<td>Study Design</td>
<td>Randomized, Prospective, Double Blind, Sham Controlled</td>
</tr>
<tr>
<td>Study Tests</td>
<td>9 Symptom Assess, 12 Neuropsych, Computerized Posture, Eye Track</td>
</tr>
<tr>
<td>Protocol Groups</td>
<td>Group A: 2.0 ATA (100% O₂ - 2.0 ATA Equivalent), 40 Sessions, 60 min Group B: 2.0 ATA (75% O₂ - 1.5 ATA Equivalent), 40 Sessions, 60 min Group C: 2.0 ATA (10.5% O₂ - 1.0 ATA Equivalent), 40 Sessions, 60 min</td>
</tr>
</tbody>
</table>
## Controversies in the Use of HBO₂
### The Current Clinical Trials

<table>
<thead>
<tr>
<th><strong>US Army MRMC Trial (24FEB2011) – Active / Recruiting</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Name</strong></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
</tr>
</tbody>
</table>
| **Sites** | Naval Hospital Camp Pendleton, CA - Portable Chamber  
Evans Army Hospital, Ft. Carson, CO - Portable Chamber  
Eisenhower Army Med. Center, Fort Gordon, GA - Fixed Chamber |
| **Inclusion Criteria** | 18-65 years old, Cohort 1 – PTSD, Cohort 2 – chronic, stable, mTBI, researcher confirmed by questionnaires / testing |
| **Study Design** | Randomized, Prospective, ± Single Blind, Sham Controlled | N = 96/24 |
| **Study Tests** | RPQ, NSI, 19 Others Secondary, Dynavision, 6-Minute Walk Test |
| **Protocol Groups** | Cohort 1(a): PTSD, No Intervention, Local Care  
Cohort 2(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 |
Controversies in the Use of HBO$_2$
The Current Clinical Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Multicenter Observational Trial Hyperbaric Oxygen Therapy in Chronic Traumatic Brain Injury or Post-Traumatic Stress Disorder (NBIRR-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Dr. James Wright &amp; Dr. Paul Harch</td>
</tr>
<tr>
<td>Sites</td>
<td>Multiple sites: currently 14 active, but number not specifically limited</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>18–65 years old, mild – moderate TBI or PTSD, diagnosis by any prior evaluation, 20% performance decrement on ANAM / “reaction time”</td>
</tr>
<tr>
<td>Study Design</td>
<td>Observational, Prospective, Unblinded, Self Control Cohort N = 1000</td>
</tr>
<tr>
<td>Study Tests</td>
<td>Not Disclosed</td>
</tr>
<tr>
<td>Protocol Groups</td>
<td>All subjects receive intervention (1.5 ATA oxygen, 60 minutes), Plan 40 sessions, but extend “as indicated” to 60 – 80 sessions</td>
</tr>
</tbody>
</table>
Controversies in the Use of HBO₂
HBO₂ for PCS – Concluding the Story

- Mild TBI is in the spotlight.
- Increasing rumors that mTBIs are more malignant than previously believed.
- Increasing rumors that treatments for symptoms associated with mTBI are ineffective.
- Increasing rumors that HBOT may offer answer.
Management of symptomatic TBI is not aimed at being “curative”
- Symptomatic Treatment
- Reassurance

HBO$_2$ (or at least pressurization or other sham) may have a role in treatment.

Multiple HBOT trials ongoing.

HBOT is not appropriate for TBI treatment based on current research evidence.
HBOT for symptomatic mTBI
Pass (on) the Gas (for now?)

Questions?