HBOT RESEARCH AND SCIENCE

MOST RECENT RESEARCH

[a] Amir Hadanny & Shai Efrati (2016): Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions, *Expert Review of Neurotherapeutics*, DOI: 10.1080/14737175.2016.1205487. Persistent post-concussion syndrome caused by mild traumatic brain injury has become a major cause of morbidity and poor quality of life. Unlike the acute care of concussion, there is no consensus for treatment of chronic symptoms. Moreover, most of the pharmacologic and non-pharmacologic treatments have failed to demonstrate significant efficacy on both the clinical symptoms as well as the pathophysiologic cascade responsible for the permanent brain injury. This article reviews the pathophysiology of PCS, the diagnostic tools and criteria, the current available treatments including pharmacotherapy and different cognitive rehabilitation programs, and promising new treatment directions. *A most promising new direction is the use of hyperbaric oxygen therapy, which targets the basic pathological processes responsible for post-concussion symptoms; it is discussed here in depth.*

[b] Baughman Shively, S., Iren Horkayne-Szakaly, Robert V Jones, James P Kelly, Regina C Armstrong, Daniel P Perl. Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series. The Lancet, Neurology, June 2016. DOI: http://dx.doi.org/10.1016/S1474-4422(16)30057-6. In what is being called a breakthrough study, Dr. Daniel P. Perl and his team at the Uniformed Services University of the Health Sciences in Bethesda, Md., [the medical school run by the Department of Defense], have found evidence of tissue damage caused by blasts alone, not by concussions or other injuries. The New York Times calls it the medical explanation for shell shock: preliminary proof of what medicine has been saying without proof for nearly 100 years -- blasts cause physical damage, and this physical damage leads to psychological problems, i.e., PTSD. The importance of this admission cannot be overstated: this is a DOD discovery with documented evidence that blast injury [IEDs, breeching, whether in training or combat, enemy and/or friendly fire] can lead directly to physical brain damage and the accompanying effects, many of which have been heretofore diagnosed as "only PTSD."

[Commentary on above: Robert F. Worth."What if PTSD is More Physical Than Psychological?," The New York Times Magazine, June 10, 2016. http://nyti.ms/1TYYp6U A new study supports what a small group of military researchers has suspected for decades: that modern warfare destroys the brain.

[Additional commentary on above]: Alexander, Caroline. "Mystery of How Battlefield Blasts Injure the Brain May Be Solved. A landmark study sheds new light on the damage caused by "blast shock"—the signature injury of wars for more than a century." *National Geographic*. JUNE 9, 2016 http://news.nationalgeographic.com/2016/06/blast-shock-tbi-ptsd-ied-shell-shock-world-war-one/

[c] Xavier A. Figueroa, PhD and James K. Wright, MD (Col Ret), USAF Hyperbaric Oxygen: B-Level Evidence in Mild Traumatic Brain Injury Clinical Trials. (IN PRE-PUBLICATION). NEUROLOGY/701565 2016. "There is sufficient evidence for the safety and preliminary efficacy data from clinical studies to support the use of HBOT in mild traumatic brain injury/ persistent post concussive syndrome (mTBI/PPCS). The reported positive outcomes and the durability of those outcomes has been demonstrated at 6 months post HBOT treatment. Given the current policy by Tricare and the VA to allow physicians to prescribe drugs or therapies in an off-label manner for mTBI/PPCS management and reimburse for the treatment, it is past time that HBOT be given the same opportunity. This is now

an issue of policy modification and reimbursement, not an issue of scientific proof or preliminary clinical efficacy."

[d] Wang F, et al. *Hyperbaric oxygen therapy for the treatment of traumatic brain injury: a meta-analysis.* Neurol Sci. 2016 Jan 8. PubMed PMID: 26746238.

"Compelling evidence suggests the advantage of hyperbaric oxygen therapy (HBOT) in traumatic brain injury. ...Patients undergoing hyperbaric therapy achieved significant improvement....with a lower overall mortality, suggesting its utility as a standard intensive care regimen in traumatic brain injury."

[e] E.G. Wolf, L.M. Baugh, C.M.S. Kabban, et al. *Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial.* UHM 2015, Vol. 42, No. 4, 2015. Dr. Wolf is a principle coauthor of the first Army study. This recent USAF paper reanalyzing the data in the cornerstone DOD/VA/Army study concludes: "This pilot study demonstrated no obvious harm [and] both groups showed improvement in scores and thus a benefit. Subgroup analysis of cognitive changes and PCL-M results regarding PTSD demonstrated a relative risk of improvement There is a potential gain and no potential loss. The VA/Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm*. . . . [emphasis added] Hyperbaric oxygen therapy for mild traumatic brain injury and PTSD should be considered a legitimate adjunct therapy if future studies demonstrate similar findings or show comparable improvement to standard-of-care or research-related treatment modalities." [NOTE: subsequent worldwide studies already published and those underway show comparable improvements.]

1. Peer-reviewed published articles

- [b] Shi XY, Tang ZQ, Sun D, He XJ. Evaluation of hyperbaric oxygen treatment of neuropsychiatric disorders following traumatic brain injury. Chin Med J (Engl). 2006;119(23):1978-82. http://www.ncbi.nlm.nih.gov/pubmed/17199942
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- [d] Lin JW, Tsai JT, Lee LM, Lin CM, Hung CC, Hung KS, et al. Effect of hyperbaric oxygen on patients with traumatic brain injury. Acta Neurochir Suppl. 2008;101:145-9. http://www.researchgate.net/publication/51416688 Effect of hyperbaric oxygen on patients with traumatic brain injury injury
- [e] Wright JK, Zant E, Groom K, Schlegel RE, Gilliland K. Case report: Treatment of mild traumatic brain injury with hyperbaric oxygen. Undersea Hyperb Med. 2009; 36(6):391-9. http://www.echa.net/36-6%20UHM-P391-399.pdf
- [f] Harch PG, Fogarty EF, Staab PK, Van Meter K. Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post traumatic stress disorder: a case report. Cases J. 2009;2:6538. http://www.ncbi.nlm.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2740054/

[g] Sahni T, Jain M, Prasad R, Sogani SK, Singh VP. Use of hyperbaric oxygen in traumatic brain injury: Retrospective analysis of data of 20 patients treated at a tertiary care centre. Br J Neurosurg. 2011. http://www.ncbi.nlm.nih.gov/pubmed/22085249

[h] Stoller KP. Hyperbaric oxygen therapy (1.5 ATA) in treating sports related TBI/CTE: two case reports. Med Gas Res. 2011;1(1):17. PMCID: 3231948. http://www.medicalgasresearch.com/content/pdf/2045-9912-1-17.pdf

[i] Paul G. Harch, Susan R. Andrews, Edward F. Fogarty, Daniel Amen, John C. Pezzullo, Juliette Lucarini, Claire Aubrey, Derek V. Taylor, Paul K. Staab, and Keith W. Van Meter. A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma. 2012 Jan 1;29(1):168-85. http://online.liebertpub.com/doi/pdf/10.1089/neu.2011.1895

[j] Rockswold, Rockswold, Zaun and Liu. A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. *Journal of Neurosurgery, Jun 2013 / Vol. 118 / No. 6 / Pages 1317-1328*http://www.ncbi.nlm.nih.gov/pubmed/23510092

2. Data from NBIRR-01 observational study

The International Hyperbaric Medical Foundation. Summary report from, "The National Brain Injury Rescue and Rehabilitation Trial – a multicenter study of hyperbaric oxygen for mild traumatic brain injury." 32 subjects improved significantly. May 2015. In pre-publication.

3. Peer-reviewed Israeli research on stroke and TBI, neurogenesis and angiogenesis

[a] Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0079995

[b] Hyperbaric Oxygen Induces Late Neuroplasticity in Post Stroke Patients - Randomized, Prospective Trial

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0053716

[C] Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury. Restor Neurol Neurosci. 2015 Oct 7. http://www.ncbi.nlm.nih.gov/pubmed/26484702

[d] Hyperbaric oxygen can induce neuroplasticity and improve cognitive functions of patients suffering from anoxic brain damage. Restorative Neurology and Neuroscience 33 (2015) 471–486 http://www.ncbi.nlm.nih.gov/pubmed/26409406

[e] Reflections on the neurotherapeutic effects of hyperbaric oxygen http://informahealthcare.com/doi/pdf/10.1586/14737175.2014.884928

4. Animal studies showing positive effects of HBOT on brain injury

[a] Blast Exposure Induces Post Traumatic Stress Disorder-Related Traits in a Rat Model of Mild Traumatic Brain Injury. Gregory A. Elder, Nathan P. Dorr, Rita De Gasperi, Miguel A. Gama Sosa, Michael C. Shaughness, Eric Maudlin-Jeronimo, Aaron A. Hall, Richard M. McCarron, and Stephen T. Ahlers. Journal of Neurotrauma. http://online.liebertpub.com/doi/abs/10.1089/neu.2012.2510

- [b] Research Report: Hyperbaric oxygen therapy improves spatial learning and memory in a rat model of chronic traumatic brain injury. Paul G. Harch, Christopher Kriedt, Keith W. Van Meter, Robert James Sutherland, BRAIN RESEARCH 1174 (2007) 120-129.

 http://www.researchgate.net/publication/5971941 Hyperbaric oxygen therapy improves spatial learning and memory in a rat model of chronic traumatic brain injury
- [c] The effect of hyperbaric oxygen on intracephalic angiogenesis in rats with intracerebral hemorrhage. Peng ZR, Yang AL, Yang QD. J Neurol Sci. 2014 May2. http://www.ncbi.nlm.nih.gov/pubmed/24836574
- [d] Kraitsy K, Uecal M, Grossauer S, Bruckmann L, Pfleger F, et al. (2014) Repetitive Long-Term Hyperbaric Oxygen Treatment (HBOT) Administered after Experimental Traumatic Brain Injury in Rats Induces Significant Remyelination and a Recovery of Sensorimotor Function. PLoS ONE 9(5): e97750. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0097750

5. Expert Opinion

"What the *Bleep* is going on with Hyperbaric Oxygen Therapy? Brain Health and Healing Foundation. Xavier Figueroa. PhD has been performing neurological clinical research since 1995 in the field of Alzheimer's research, as well as basic research in neuron biology, cancer research, bioengineering and the biophysics of water in cells. He has a long history of involvement with research using hyperbaric oxygen therapy for brain injury.

- **http://brainjury.org/blog/2014/05/01/what-the-bleep-is-going-on-with-hyperbaric-oxygen-therapy/
- **http://brainjury.org/blog/2014/07/03/what-the-bleep-is-wrong-with-the-dodva-hbot-studies/
- **http://brainjury.org/blog/2014/11/23/what-the-is-going-on-with-hyperbaric-oxygen-therapy-part-3/

UHM 2012, Vol. 39, No. 4 – How many deaths will it take? AN EDITORIAL PERSPECTIVE. Undersea & Hyperbaric Medical Society, Inc. *How many deaths will it take till they know?* Monkeys, madmen and the standard of evidence. George Mychaskiw II, DO, FAAP, FACOP, Editor-in-Chief Chair, Department of Anesthesiology, Nemours Children's Hospital, Orlando, Florida USA. The Journal of Hyperbaric Medicine is the most prestigious journal on Hyperbaric Medicine in the world. "Hyperbaric oxygen is a safe, easily used treatment that, in many cases, has resulted in a dramatic improvement in the symptoms of patients with [TBI]. Every day we are.... gathering more data validating its efficacy.... I feel , as do many of my colleagues, that there is sufficient clinical and research evidence to justify the use of [HBOT] as a standard-of-care treatment for [TBI] that should be reimbursed by CMS and Tricare.... I have no doubt that, over the next several years, [HBOT] will be proven beyond a reasonable doubt to be one of the most effective treatments for [TBI].... There is a preponderance of evidence now to justify the use and funding for the treatment...." http://www.therapiehyperbare.com/images/hyperbare/2012-06_uhms_editorial.pdf

Chamber of Hopes for Brain Repair. Eshel Ben-Jacob , PhD. January, 27, 2013. http://www.assafh.org/sites/en/Documents/Chamber%20of%20Hopes%20for%20Brain%20Repair.pdf

6. Data from DoD/Army studies, with responses

Summary of positive findings in Army Studies: Army medicine has run trials investigating the use of Hyperbaric Oxygen to treat and help heal Traumatic Brain Injury. They have shown that HBOT is both safe and effective: "Randomization to the chamber offered statistical and in some measures clinically significant improvement over local routine TBI care." Also: ".... total scores for [both] groups revealed significant improvement over the course of the study for both the shamcontrol group and the HBO2 group....." Expert outside consultants to DOD declared that "[HBOT] is a healing environment."

- [a] Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma. 2012;29(17):2606-12. (DoD) (USA) http://biawa.org/docs/pdf/MTBI%20PCS%20J%20Neurotrauma%202012.pdf
- [b] Paul G. Harch, MD. Letters to the Editor. Journal of Neurotrauma. Hyperbaric Oxygen Therapy for Post-Concussion Syndrome: Contradictory Conclusions From a Study Mischaracterized as Sham-Controlled. 2014 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3837504/
- [c] Cifu DX, Hart BB, West SL, Walker W, Carne W. The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms. J Head Trauma Rehabil. 2013. (DoD) (USA) http://journals.lww.com/headtraumarehab/Fulltext/2014/01000/The_Effect_of_Hyperbaric_Oxygenton_Persistent.2.aspx
- [d] Weaver LK, Cifu D, Hart B, Wolf G, Miller RS. Hyperbaric oxygen for post-concussion syndrome: Design of Department of defense clinical trials. Undersea Hyperb Med 2012; 39(4); 807-814.
- [e] Paul G. Harch, MD. Letters to the editors, UHM 2013, Vol. 40, No. 5 LETTERS. Department of Defense trials for hyperbaric oxygen and TBI: Issues of study design and questionable conclusions. http://www.ncbi.nlm.nih.gov/pubmed/24224289
- [f] 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. DoD/USA http://nnr.sagepub.com/content/28/5/420
- [g] Cifu DX, Walker WC, West SL, Hart BB, Franke LM, Sima A, et al. Hyperbaric oxygen for blast-related postconcussion syndrome: Three-month outcomes. Ann Neurol. 2014;75(2):277-86. (DoD) (USA). Available upon request.
- [h] Army Trials Report from UHMS Conference, June 2013. Press Release: "DoD announces results of first three DoD-Sponsored trials using hyperbaric oxygen for mild traumatic brain injury." Available upon request.
- [i] R. Scott Miller, M.D., COL, US Army, Director, Hyperbaric Oxygen Research Program, US Army Medical Materiel Development Activity, Ft. Detrick, MD. *Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members With Persistent Postconcussion Symptoms. JAMA Intern Med.* doi:10.1001/jamainternmed.2014.5479. Published online November 17, 2014.

7. Validating SPECT Scans to diagnose HBOT treatment before-and-after brain states

Raji CA, Tarzwell R, Pavel D, Schneider H, Uszler M, et al. (2014) Clinical Utility of SPECT Neuroimaging in the Diagnosis and Treatment of Traumatic Brain Injury: A Systematic Review. PLoS ONE 9(3): e91088. doi:10.1371/journal.pone.0091088

8. BLAST INJURY BIBLIOGRAPHY

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Baughman Shively, S., Iren Horkayne-Szakaly, Robert V Jones, James P Kelly, Regina C Armstrong, Daniel P Perl. *Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series*. The Lancet, Neurology, June 2016. DOI: http://dx.doi.org/10.1016/S1474-4422(16)30057-6.

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Mac Donald, CL; Ann M. Johnson; Linda Wierzechowski; Elizabeth Kassner, Theresa Stewart, Elliot C. Nelson, Nicole J. Werner, David Zonies, John Oh, Raymond Fang, David L. Brody. *Prospectively Assessed Clinical Outcomes in Concussive Blast vs. Nonblast Traumatic Brain Injury Among Evacuated US Military Personnel*. JAMA Neurol. Published online June 16, 2014. doi:10.1001/jamaneurol.2014.1114

Miller KJ, Ivins BJ, Schwab KA (2013) *Self-Reported Mild TBI and Postconcussive Symptoms in a Peacetime Active Duty Military Population: Effect of Multiple TBI History Versus Single Mild TBI*. J Head Trauma Rehabil 28:31–38, doi:10.1097/HTR.0b013e318255ceae

Omalu B, Hammers JL, Bailes J, Hamilton RL, Kamboh MI, Webster G, Fitzsimmons RP (2011) Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. Neurosurg Focus 31:E3, doi:10.3171/2011.9.FOCUS11178 Reimers, SD and Slade, JB. The Case for Transient Air Embolism from Lung Injury as a Mechanism for Blast—Related Brain Injury and Its Implications. May 2015. Correspondence.

Rosenfeld, JV Alexander C McFarlane, Peter Bragge, Rocco A Armonda, Jamie B Grimes, Geoffrey S Ling. *Blast-related traumatic brain injury*. Lancet Neurol 2013; 12: 882–93. July 22, 2013. http://dx.doi.org/10.1016/S1474-4422(13)70161-3

Ryu, Jiwon, Iren Horkayne-Szakaly, Leyan Xu, Olga Pletnikova, Francesco Leri, Charles Eberhart, Juan C Troncoso and Vassilis E Koliatsos. *The problem of axonal injury in the brains of veterans with histories of blast exposure*. Acta Neuropathologica Communications 2014, 2:153 http://www.actaneurocomms.org/content/2/1/153.

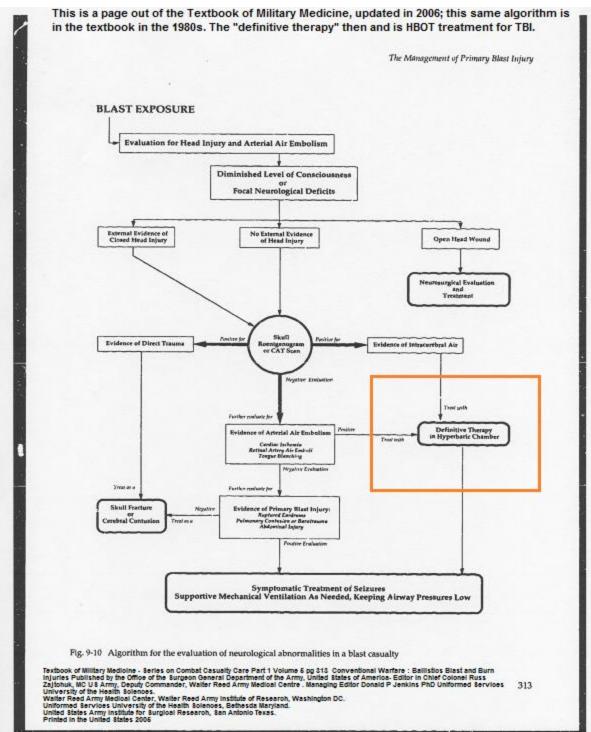
Trotter,BB, Meghan E. Robinson, William P. Milberg, Regina E. McGlinchey and David H. Salat. *Military blast exposure, ageing and white matter integrity*. BRAIN, June 1, 2015. doi:10.1093/brain/awv139

Worth, RF, *What if PTSD Is More Physical Than Psychological?* A new study supports what a small group of military researchers has suspected for decades: that modern warfare destroys the brain. New York Times, JUNE 10, 2016.

Johns Hopkins reports that the brains of Iraq and Afghanistan combat veterans who survived blasts from improvised explosive devices and died later of other causes show a honeycomb of broken and swollen nerve fibers in critical brain regions, including those that control executive function. The pattern is different from brain damage caused by car crashes, drug overdoses or collision sports, and may be the never-before-reported signature of 'shell shock' suffered by World War I soldiers.

http://www.sciencedaily.com/releases/2015/01/150114140600.htm

Blast injury, and the accompanying role of air embolism in invisible wounds to the brain, is still not widely studied and thus seldom treated. Hyperbaric Oxygen Therapy is recognized worldwide as the definitive treatment for air embolism. Air/gas embolism is already an on-label, approved indication for HBOT.



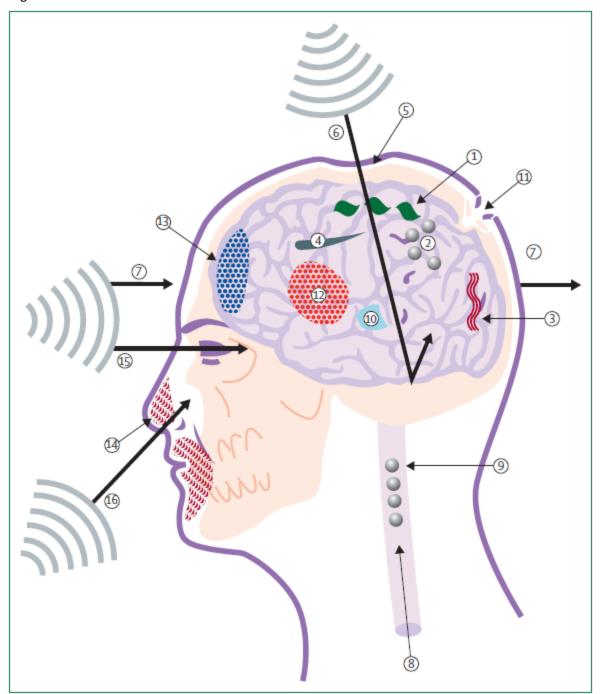


Figure 1: Schematic diagram of the mechanisms of blast-related traumatic brain injury

Figure shows local effects (1–7) and systemic effects (8, 9) of primary blast injury, secondary blast injury (10–12), tertiary blast injury (13), quaternary blast injury (14), and portals for blast wave transmission to the brain (15, 16). (1) Acoustic impedance mismatch causes spallation. (2) Shock-bubble interaction. (3) Shear stress causing diffuse axonal injury. (4) Cavitation. (5) Skull deformation with elastic rebound. (6) Reflection of the blast wave within the skull. (7) Bobblehead effect of acceleration-deceleration. (8) Blood surge from the torso damages the microvasculature. (9) Air embolism from blast lung injury.(10) Penetrating fragments. (11) Compound fractured skull. (12) Intracerebral haemorrhage. (13) Contrecoup contusion. (14) Burns. (15) Blast wave transmitted through the orbits. (16) Blast wave transmitted through the nasal sinuses.

Blast-related traumatic brain injury. Jeffrey V Rosenfeld, et al *Lancet Neurol* 2013; 12: 882–93 July 22, 2013 http://dx.doi.org/10.1016/S1474-4422(13)70161-3

14 on-label indications for HBOT are already approved and insured

- 1. Air or Gas Embolism**
- 2. Carbon Monoxide Poisoning**

Carbon Monoxide Poisoning Complicated By Cyanide Poisoning

- 3. Crush Injury, Compartment Syndrome and Other Acute Traumatic Ischemias**
- 4. **Decompression Sickness****
- 5. Arterial Insufficiencies:

Central Retinal Artery Occlusion**

Enhancement of Healing In Selected Problem Wounds

- 6. Clostridial Myositis and Myonecrosis (Gas Gangrene)
- 7. Severe Anemia
- 8. Intracranial Abscess
- 9. Necrotizing Soft Tissue Infections
- 10. Osteomyelitis (Refractory)
- 11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
- 12. Compromised Grafts and Flaps
- 13. Acute Thermal Burn Injury
- 14. Idiopathic Sudden Sensorineural Hearing Loss (Approved on October 8, 2011 by the UHMS Board of Directors)

** These indications are similar to conditions found in brain injury

