

#1 What the *Bleep!* is Going on With Hyperbaric Oxygen Therapy?

by **Xavier A. Figueroa, Ph.D.**

When I meet with friends, relatives and work colleagues, I get asked about what I do. When I explain my job, I always get asked, “Does hyperbaric oxygen therapy really work for traumatic brain injury?”

I know many of those who are reading this blog have the same question in mind. It’s a pretty important question for a person that has a TBI.

So – does it work or not?

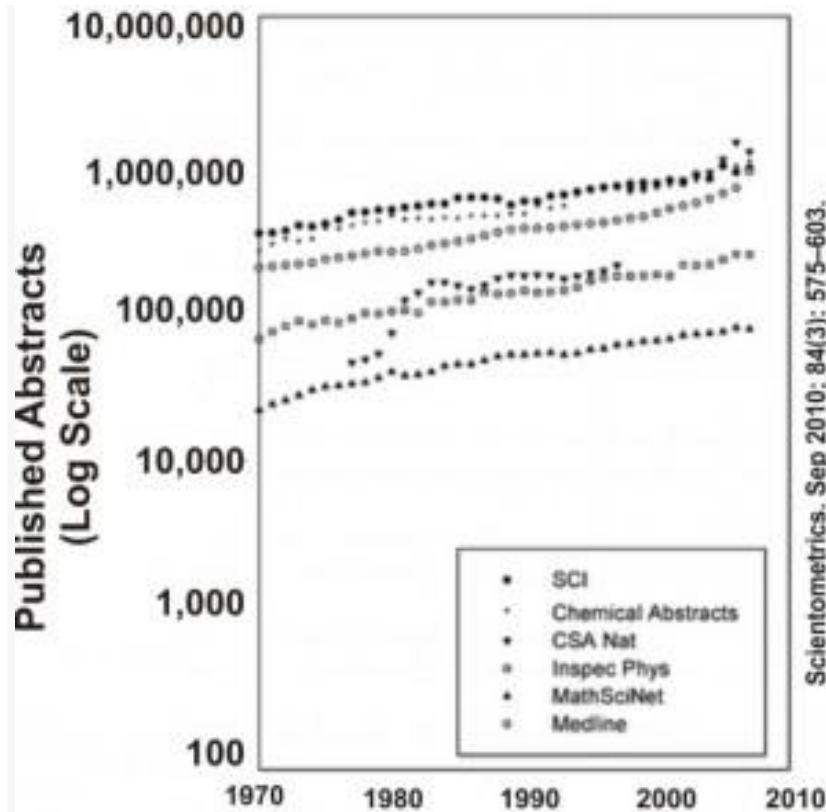
In my opinion, yes.

But opinions are like belly-buttons, everyone has one. What you really need are facts and studies that support your opinion (if you are impatient to find them, jump [HERE](#)). Now, me saying that HBOT can help treat a TBI will probably raise a few eyebrows. Let’s face it, neurologists, psychiatrists and researchers have been going after this problem for decades. Me saying that a pressurized gas can heal the ravages of a traumatic brain injury may sound far-fetched. But you don’t know what I know... and neither do a lot of highly-trained doctors.

You see, doctors are the problem. And the solution to getting HBOT as a therapy approved.

After finishing a 4-year baccalaureate program in college, medical school takes another 4 years to complete. In school you sample different specialties (family medicine, emergency medicine, etc.) and it then takes another 3 – 7 years of residency/fellowship to complete a specialty. On average, doctors are exposed to 3 – 4 days of education of hyperbaric medicine in their general training. This training does not include the current research, only the well-established treatments. In all, not much exposure or education is given to doctors-in-training for hyperbaric medicine.

After graduation, a doctor needs to maximize the number of patients and billable procedures’ he or she can accomplish. Med school started getting really expensive in the 1980’s. This means that doctors are busy people and specialized in the area of medicine that they practice and keeps them employed.



Doctors keep current in their

specialty by joining general medical societies (The American Medical Association) and societies that cater to their specialties (American Academy of Neurology, for example). The amount of information out in the medical research journals is humongous, even within specialties.

And it just keeps growing.

A lot.

The graph on the right shows the growth rate for the past 30 years for medical and scientific papers. And it is not going to slow down any time soon. Separating the metaphorical chaff from wheat isn't easy, either.

Finding the time to read, let alone keep up, is a daunting and time consuming task. So doctors, like most of us, rely on experts and opinion leaders to keep them informed. Usually they gather at conferences to discuss the burning issues and emerging problems that affect their specialty.

Doctors and patients are also relying on comments and opinions from trusted sources. Comments on research, [such as the one below](#), are normally provided by trained medical providers, who are non-experts in the field of hyperbaric medicine and have a passing knowledge of the research literature:



Journal Watch

Jonathan Silver,
MD

Associate Editor
PSYCHIATRY



Hyperbaric Oxygen Therapy for Mild TBI: Save Your Time and Money

Jonathan Silver, MD reviewing Wolf G et al. J Neurotrauma 2012 Nov 20.

I'm sure that Dr. Silver is an excellent Psychiatrist (the New England Journal of Medicine has a reputation for selecting excellent doctors), but his specialty or training is not hyperbaric medicine (although he does do research on [TBI and pharmaceuticals](#)). The details and nuances of hyperbaric oxygen play a big part in understanding technical information and getting the right conclusions out of data. **This will become very relevant when we discuss the Department of Defense sponsored studies.**

More importantly, the impact that a specialty has depends on the size of the membership and what illness it treats. So, let's see what the different populations of doctors in each specialty are in the US. The chart below is the number of active physicians (MD's and DO's) as of 2012 in each of the specialties below (the data was compiled from the Henry J. Kaiser Family website and the American Academy of Neurology website). The largest single group is Psychiatry, which coincidentally is the specialty that handles the majority of TBI management. At the extreme end is Hyperbaric Medicine, with about 2,000 active specialists in the US.

Psychiatry	Surgery	Anesthesia	Emergency Medicine	Cardiology	Neurology	Oncology (Cancer)	Hyperbaric Medicine
47,282	45,291	43,662	41,479	27,076	18,180	14,649	~2,000

Hyperbaric medicine is a very small specialty compared to any of the other specialties. It mostly focuses on wound treatment, skin burns and difficult to treat infections. They have no lobbying arm in Congress and the average NIH budget for HBOT research is less than \$2 million/year.

Alzheimer's disease averages \$450 million and TBI research average \$90 million (information was from the [NIH website](#)).

So, why don't you hear about HBOT in a positive light? Those who have the membership (and money) have bigger bullhorns and access to funding institutions. Hyperbaric medicine is tiny and underfunded.

What A Little Digging around Shows

The biggest complaint that is tossed around by many physicians is the lack of data showing the effectiveness of HBOT for traumatic brain injury. Point granted...but only if you ignore the literature.

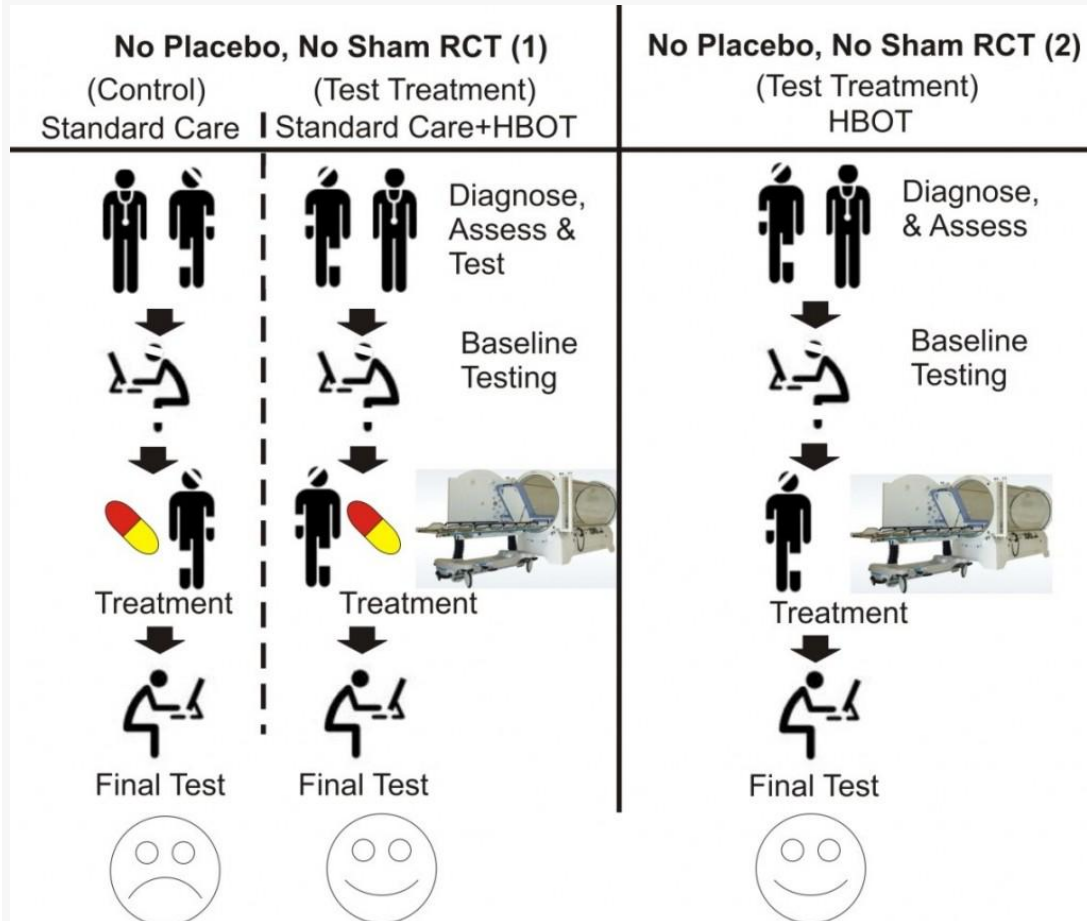
There are several papers (some are case reports, other are observational studies) that show the effect that HBOT has on diagnosed traumatic brain injury. All are uniformly positive, many with long-term maintenance of recovery and with mild to no side effects from the treatments on humans.

These reports are listed below:

1. 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.
2. Hardy P, Johnston KM, De Beaumont L, Montgomery DL, Lecomte JM, Soucy JP, et al. Pilot case study of the therapeutic potential of hyperbaric oxygen therapy on chronic brain injury. *J Neurol Sci*. 2007;253(1-2):94-105.
3. 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.
4. 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.
5. 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.
6. 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.
7. Stoller KP. Hyperbaric oxygen therapy (1.5 ATA) in treating sports related TBI/CTE: two case reports. *Med Gas Res*. 2011;1(1):17. PMID: 3231948.
8. 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.

From these eight reports, a total of 396 human subjects were enrolled. Some studies did only 2 treatments of HBOT. Other did over 100 treatments. All used 1.5 atmospheres in pure Oxygen. The studies are designed around two types of testing systems: 1) split study subjects into groups that

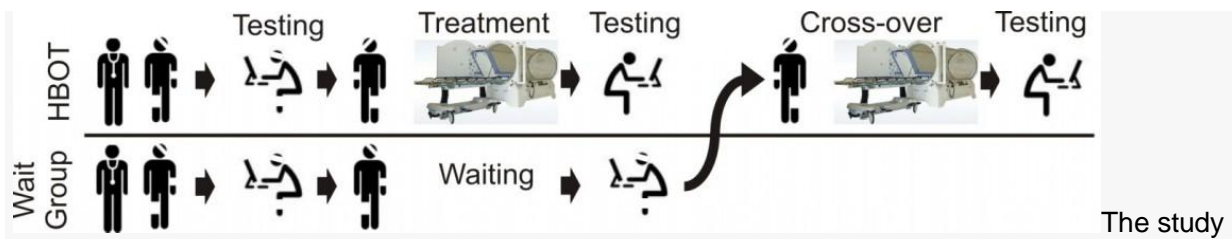
received standard treatments for TBI or standard treatments for TBI plus HBOT; 2) Measure performance before HBOT and then after HBOT in study participant with long-standing TBIs (greater than 2 years). All saw improvements that were statistically significant.



At this point,

the usual chorus of “but these are not [randomized](#), [placebo](#) or [sham](#) controlled clinical trials (RCTs)” comes up (if you need a definition for a randomized, controlled trial, click [here](#)). All true, except that other drugs or treatments have been accepted into the medical mainstream without placebo/sham RCTs. Penicillin is just one example. In any event, randomized placebo controlled clinical trials are not the end-all, be-all in medical research. Plenty of clinically relevant data can be gotten with a cross-over RCT, such as the one below.

1. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury – Randomized Prospective Trial. PLoS One. 2013;8(11):e79995. (CIVILIAN) (ISRAEL)



by Boussi-Gross (depicted above) showed a statistically significant difference before and after treatment for the HBOT group after forty, 1.5 ATA treatments. A total of 32 study participants were in the HBOT treatment group, while 24 study participants were assigned to the wait group. In total, 56 study subjects were treated with HBOT. The wait group showed no statistically significant changes in their test results during the 2 months that the HBOT group was treated. After the wait group was treated with HBOT (or crossed-over to the treatment), the wait group improved as much as the HBOT treatment group.

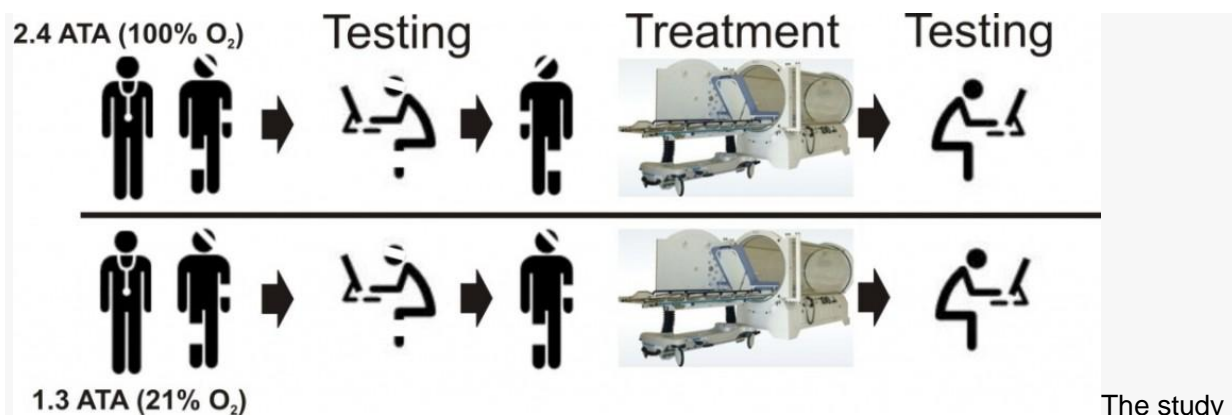
Pretty clear cut. HBOT works for the treatment of mTBI at 1.5 ATA.

The Other Results

But what about all those Department of Defense (DoD) funded studies!? I mean, these are big budget, well controlled and thoroughly vetted studies done by the Armed Forces medical and research division of the United States of America. Those are REAL studies, sham RCTs! And they showed that HBOT does not help with TBI.

Or did they?

1. 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)



by Wolf et al. is one of the few studies to use a [sham](#) treatment in HBOT. Also, for the first time a

higher pressure regime was used (2.4 ATA) than the traditional 1.5 ATA used for mTBI. Now, a sham is suppose to be a treatment or procedure that does not produce an improvement...it should be flat...unless there is a placebo effect. The only way you can establish a placebo effect is to absolutely rule out that your treatment (or drug) produces a biological activity. That's a hard thing to do with oxygen, since it is always biologically active. Explaining why oxygen cannot be used as a placebo is a separate blog post (stay tuned for the next post...I promise to make it fun...really...about oxygen).

In any case, both exposures produced changes (improvements) in symptoms measured in the PCL-M (Post-Traumatic Disorder Check List-Military) for these service members.

Which one produced the best outcomes: the 1.3 ATA or the 2.4 ATA?

Out of the 22 symptoms that were measured, 9 significantly improved under air treatment at 1.3 ATA. The 2.4 ATA treatment produced one significant improvement in a symptom. If this was a placebo effect (a psychological effect), the number of improvements and the magnitude of the improvements should have been equal across the board for both pressures. Only the sham treatment had such a lopsided improvement for the study participants.

Why would a “sham” produce a better outcome?

The sham increased oxygen concentration anywhere from 28-43% above normal (pressure in the sham were in the range of 1.3ATA to 1.2 ATA). Any increase in dissolved oxygen in the body can produce (under pressure) a measurable biological response (I'm saving the explanation for the next blog post...honest). Dosages of oxygen are as real as dosages of pills. Too much of a drug can harm you, too little will do nothing...just right will treat what is ailing you. Oxygen under pressure is no different than a pill.

And the conclusions by Wolf et al. is the following:

“The current study in participants with postconcussive syndrome from chronic mTBI demonstrates no efficacy in symptom relief with HBO2 at an exposure pressure of 2.4 ATA for 90 min given once daily for 30 treatments; however, both groups improved more than would be expected greater than 6 months after mTBI. It is recommended that larger, multicenter, randomized, controlled (both sham-control and wait-list), double-blinded clinical trials be

conducted at lower total oxygen doses as recommended by AHRQ.”

Dr. Wolf is an experienced MD, trained in the field of hyperbaric medicine. He is an Air Force officer (Colonel) and a careful clinician. He is being a scientist when ascertaining the facts of the study. In this case he has drawn conclusion from his two test parameters (1.3 ATA, Air; 2.4 ATA 100% Oxygen)...they were not sufficiently different from one another to reach statistical significance. The improvements seen in both groups were not statistically significant when 1.3 ATA was compared to 2.4 ATA. Let that sink in for a minute...both groups improved sufficiently to be statistically significant from their starting (baseline) values, but not different enough between both groups to register as significant.

That was all Dr. Wolf and his colleagues could conclude.

And he acknowledge that the improvements were greater than expected with chronic mTBI study participants. More studies are needed, with better controls in order to reach a solid conclusion.

So, did this study conclude that HBOT is ineffective for mTBI?

No.

Pressurized air (at 1.3 ATA) appears to alleviate more symptoms of a chronic TBI better than pure oxygen (at 2.4 ATA). The statistics from before treatment and after treatment bear it out.

And it showed that HBOT is safe for individuals with a TBI...even at pressures as high as 2.4 ATA.

OK. But What About the Other Studies?

The other DoD studies, which were going in parallel or right after the Wolf study, came to a different conclusion for their results. The analysis of these three published articles will take quite a while to explain, so I will go into detail on my next blog post (oh yeah...along with how oxygen works you will get a detailed analysis of these three studies...two-for-one...lucky you). But at least these three studies concluded the same thing as the Wolf et al. studies...HBOT is safe for individuals with a TBI.

1. 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)
2. 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)

3. 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)

Oh... and the DoD funded studies are the few studies that fail to show any improvement of TBI symptoms with HBOT. The majority of civilian studies (from four countries and seven independent civilians clinical groups) have shown positive outcomes.

Parting Thought for Those Affected

I have worked with physicians trained in HBOT, run clinical research with HBOT and seen first-hand the effects of HBOT on people suffering from the long-term effects of traumatic brain injury (TBI). The majority of folks that undergo HBOT improved to a surprising degree. A small minority does not improve...and we don't know why. We would love to find out.

Now, my opinion on HBOT is that it works to treat neurological injuries based on clinical research I have performed, review of the literature and my training as a Ph.D. (Neurobiology/Toxicology). I have no financial interest in HBOT; it's actually costing me money, time and career advancement to be a proponent, let alone a researcher in this field.

So, why do I do it? Well, to put it simply, it works. And there are many people that are living better lives because they have undergone treatment with HBOT for a TBI. When there is a treatment that can work for TBI, training TBI victims to cope with a "new normal" as a standard of care is getting very close to malpractice. Unfortunately, there is a lot of information out there that can trip up a well-trained physician but the reliance on authority or experts as a guide to treatment is a poor substitute for firsthand experience.

Fortunately there are a growing number of physicians (MD's, DO's, NP's and clinical PhD's) that are recognizing the limitations of pharmaceutical, psychological and psychiatric methods for rehabilitation. They are looking for alternatives to help their patients. They are finding positive results with HBOT.

You see, I was not a proponent of HBOT when I first jumped into this field in 2010. Like many medical practitioners and researchers, I thought that HBOT might be useful for only a few things in medicine (decompression sickness, wound treatment and the like) but treating neurological conditions? It's only a gas under pressure. How could it work?

Glad you asked. We'll see how in the next blog post, too.

“While we applaud good science, there comes a point [...] of stagnation as the standard of evidence required for the blessing of organized medicine exceeds reality (where most of us live).”

– George Mychaskiw II, DO, FAAP, FACOP,

UHM 2012, Vol. 39, No. 4 – **How many deaths will it take? AN EDITORIAL PERSPECTIVE**

Definitions:

Placebo: (Science: pharmacology) Any dummy medical treatment, originally, a medicinal preparation having no specific pharmacological activity against the patients illness or complaint given solely for the psychophysiological effects of the treatment, more recently, a dummy treatment administered to the control group in a controlled clinical trial in order that the specific and non-specific effects of the experimental treatment can be distinguished i.e., the experimental treatment must produce better results than the placebo in order to be considered effective. An innocuous or inert medication; given as a pacifier or to the control group in experiments on the efficacy of a drug. An inactive substance given to a patient to satisfy an apparent psychological need.

(<http://www.biology-online.org/dictionary/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. (<http://www.merriam-webster.com/medical/sham>).

RCT: A randomized controlled trial (or randomized control trial; RCT) is a specific type of scientific experiment, in which study subjects, after assessment of eligibility and recruitment, but before the intervention to be studied begins, are randomly allocated to receive one or other of the alternative treatments under study (http://en.wikipedia.org/wiki/Randomized_controlled_trial).

Cross-over RCT: Randomized, controlled crossover experiments are especially important in health care. In a randomized clinical trial, the subjects are randomly assigned to different arms of the study which receive different treatments. When the randomized clinical trial is a repeated measures design, the same measures are collected multiple times for each subject. A crossover clinical trial is a repeated measures design in which each patient is randomly assigned to a sequence of treatments, including at least two treatments (of which one "treatment" may be a standard treatment or a placebo) (http://en.wikipedia.org/wiki/Crossover_study).

Related

[What the Is Wrong with the DoD/VA HBOT Studies?!](#) July 3, 2014 In "brain"

[What the Is Going On With Hyperbaric Oxygen Therapy?! \(Part 3\)](#) November 23, 2014 In "brain"

[Veterans Have Seen This Before: Memories of Vietnam?](#) November 19, 2013 In "Dept of Defense"

#2 What the <#\\$*&!> Is Wrong with the DoD/VA HBOT Studies?!!

Xavier A. Figueroa, Ph.D.



National Museum of Health & Medicine

The iron lung was a desperate and ingenious solution for the ravages of polio. It allowed those infected and affected by the polio virus to continue to live, even with the loss of nerve function to their diaphragm.

It was only with the development of mass vaccination campaign against polio that the iron lung was made obsolete or rare.

Vaccination was once thought to be unscientific, unproven and dangerous technology, yet it is standard today and has saved the lives of billions of people. HBOT is at a similar cross-road with the treatment for TBI.

For all of you that have come back to follow up on the last blog post, thanks for sticking around. For the new people here, it might be worthwhile to go back to our first post in this series [here](#).

Here we are, back at it again, trying to understand what the *bleep* is going in with hyperbaric oxygen therapy (HBOT).

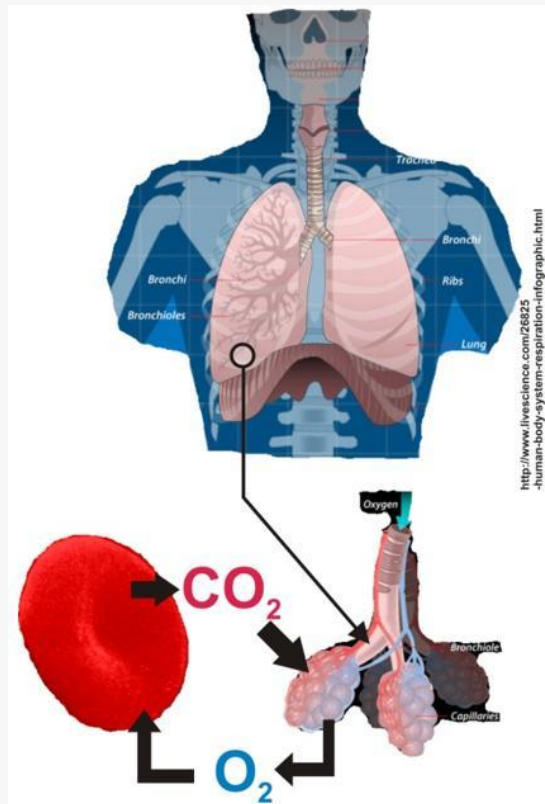
On the last blog post, I mentioned that we were going to discuss two major topics:

1. The relevant biological data on how hyperbaric oxygen therapy (HBOT) works.
2. The three remaining DoD studies using HBOT to treat traumatic brain injury.
 - a. 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)
 - b. 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)
 - c. 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)

Now, before I get started, the intent of these blog posts is to provide as clear an analysis of the existing data on HBOT used for brain injury as possible (without having anyone fall asleep!). We are here to simplify, teach and untangle the morass of studies, spin and myths that have arisen over time with HBOT, and have a little fun in the process.

Onwards to the nerdy but fundamental stuff!

The Effects of Hyperbaric Oxygen on the Body



What do we breathe, day in and day out? It is a mix of Oxygen/Nitrogen at roughly 21%/79%. Every cell in our body utilizes oxygen to metabolize (build, destroy and maintain). Oxygen is an essential metabolic component that is used in over +5,000 unique pathways in the body. We even have a very elegant and complex system to capture oxygen from the air (our lungs and the red blood cells; see image below).

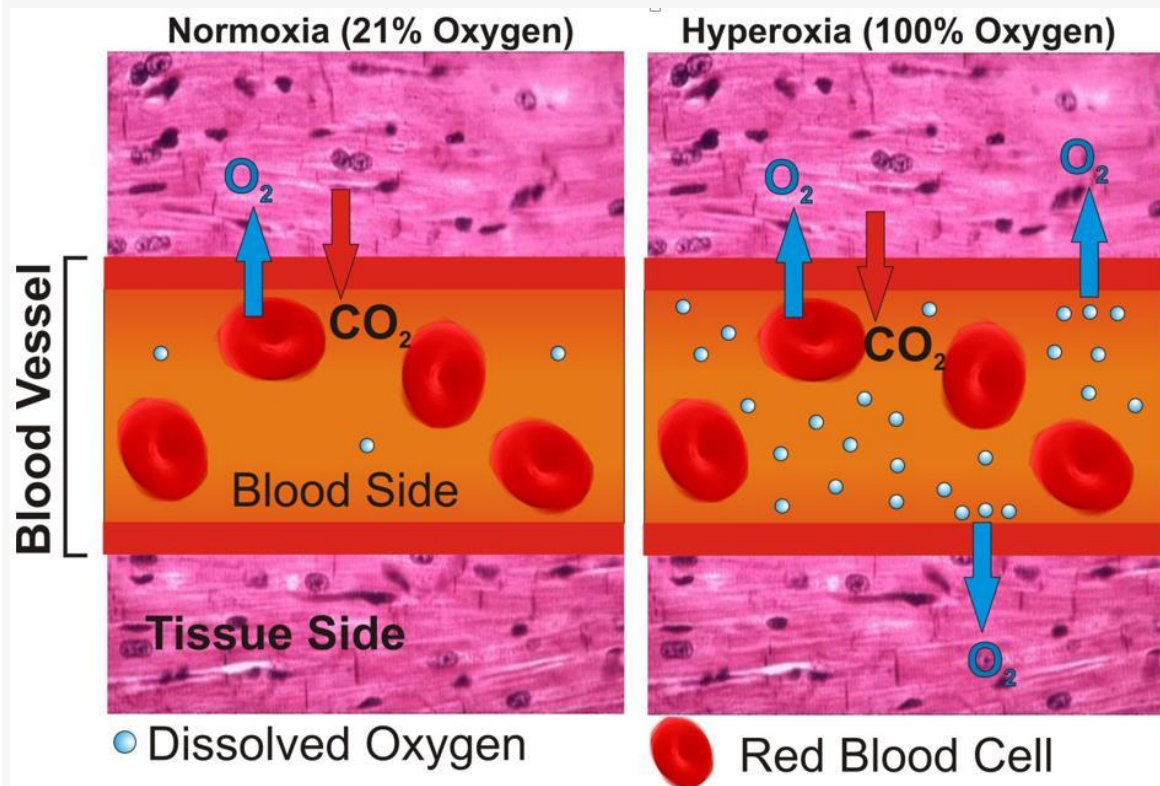
Red blood cells in our body are specialized oxygen capturing cells. They are completely dedicated to do two things: capture oxygen from the lungs and remove carbon dioxide from the body. All the oxygen that our cells use is delivered by the red blood cells under normal circumstances.

In healthy adults and children, the red blood cells are 97-98% saturated with oxygen. When we breathe pure oxygen (100% oxygen versus air), we can reach 99% saturation levels. The only know and safe method to increase oxygen levels in the body is through hyperbaric oxygen.

For those that want a little more detail on how HBOT works, you can go to our very first blog post [here](#).

In the simplest terms possible, an HBOT chamber works in the same way a soda water maker works: It dissolves a gas into the water of the body! In the case of an HBO chamber, the gas is 100%, USP Medical grade oxygen.

When you dissolve oxygen into the water portion of the body (the plasma), you are adding to the overall amount of oxygen that can be delivered into the tissues. Why? Remember that in order for us to live and breathe, we need the red blood cells to deliver the oxygen to our tissues. Very little oxygen is dissolved into the plasma of the blood under normal circumstances (At sea level, where pressure is 1.0 ATA, we breathe 21% Oxygen/79% Nitrogen. That is “normal”). When we increase the pressure and/or increase the amount of oxygen, we can increase the amount of dissolved oxygen in the plasma. This increase allows for more oxygen to reach the tissues.



How much difference can there be when we breathe in a pressurized environment? Well, quite a bit.

Hemoglobin has an upper limit in the amount of oxygen it can carry. The theoretical maximum, if the red blood cells were 100% saturated (they never are) would be 203 mL oxygen/L of blood (Upper half of Table 1). Even with increases in the amount of oxygen and pressure, hemoglobin has a finite carrying capacity for oxygen. All the excess oxygen is provided by the dissolved fraction in the plasma (the lower half of Table 1). Even a modest pressure increase of 1.5 ATA (the equivalent

pressure experienced underwater at 16 feet) increases the total amount of oxygen to the tissues to 228 mL Oxygen/L blood (a 14% increase in total oxygen).

Gas Mix	Source	Pressure (ATA)	mL Oxygen/Liter blood
1.0 (21% Oxygen/79% Nitrogen)	Red Blood Cells	1	196
1.0 (100% Oxygen)	Red Blood Cells	1	198
1.5 (100% Oxygen)	Red Blood cells	1.5	200
2.0 (100% Oxygen)	Red Blood cells	2	201
3.0 (100% Oxygen)	Red Blood Cells	3	203
Plasma			
1.0 (21% Oxygen/79% Nitrogen)	Plasma	1	3.2
1.0 (100% Oxygen)	Plasma	1	17
1.5 (100% Oxygen)	Plasma	1.5	28
2.0 (100% Oxygen)	Plasma	2	37
3.0 (100% Oxygen)	Plasma	3	56

What does the body do with that increase in oxygen? A lot.

- Increases the production of stem cells (both local and global) [1-13].
- Induces a state of analgesia (hyperbaric treatments reduce the sensation of pain) [14-18].
- Inhibits inflammation (HBOT stops inflammatory cells from entering the site of injury) [19-26].
- Reduces swelling (HBOT causes blood vessels to constrict, reducing edema) [27-30].
- Protects cells from dying (inhibits apoptosis and necrosis) [31-37].
- Promotes new blood vessel growth (angio- and vasculogenesis) [5, 38-47].
- Increases cellular metabolism [48-54].
- Accelerates bone knitting and wound healing [41, 55-65].
- Increases the number of enzymes that stop reactive oxygen species (oxygen radicals) [66-72].

Most of the effects we see with HBOT are due to signaling from reactive oxygen species (OH⁻, NO[•], H₂O₂), changes in gene/protein expression and increased mitochondrial respiration. The production of oxygen radicals are essential for the effects we see in HBOT as they are the signals for cells to adapt or change. Other effects are still not fully understood, such as why HBOT increases red blood cell rigidity and blood viscosity [73, 74]. Hyperbaric oxygen induces a profound change in cell behavior, gene expression and healing, all by increasing the total amount of oxygen in the body and the pressure exerted on cells.

Going the Other Way With Oxygen

So, if we see a reduction in oxygen concentration, do we see biological effects on the body, too?

Absolutely!

Hypoxia is the term used when the overall oxygen level drops below 21% or the atmospheric pressure is less than 1.0 ATA (with 21 % oxygen). Hypoxia induces a number of changes in the body, mostly to counteract the loss of oxygen, such as an increase in red blood cells [75-78] and the switching of gene expression in blood cell precursors [79] that are better able to grab oxygen.

Hypoxia has been used to prepare high performance athletes in endurance training [80] and may have reparative properties in preconditioning. Indeed, preconditioning may induce protection against other injuries such as stroke and TBI [81]. The role of oxygen is diverse and still poorly understood.

The reason to bring up hypoxia in this blog post is to demonstrate a simple fact: The body and brain are sensitive to changes in oxygen concentration. It is this ability to respond to those changes that makes HBOT such a powerful treatment tool. More important to the discussion, is the fact that a placebo or shams are nearly impossible to simulate with HBOT trials, let alone with a pressure treatment of any kind.

How Much Oxygen/Pressure Is Enough?



Wait a minute?!!

Did you say it is nearly impossible to simulate a sham treatment?

Yes. Cells in the body are finely attuned to changes in oxygen concentration and pressure changes.

As we have seen, changes in oxygen concentration and gas pressure can affect the body. But how much is required to show a detectable level of change? The Wolf et al. study [82] showed that modest changes in pressure (an increase of 0.2-0.3 ATA) with 21% Oxygen was sufficient to improve symptoms associated with a TBI. Remember that the oxygen dose in the "sham" dissolved ~30% more oxygen into the plasma than just breathing room air. This was enough to induce a significant change in symptoms scores in two independent assessment scales.

In the research literature, changes smaller than 0.1 ATA have induced growth factor production and an increase in cell division [83] in epithelial cell cultures when compared to the control cultures. Studies of smooth muscle cells derived from human aorta reported that 1.1 ATA of room air (an increase of 0.1 ATA) was sufficient to increase growth rates [84, 85]. Cells can sense these subtle changes.

The cell culture data is supported by evidence from studies of lung function and oxygenation with chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis and pulmonary hypertension (thromboembolic). Moving patients from cities located 800 meters above sea-level (0.91 ATA) to locations 400 meters below sea-level (1.05 ATA) improved oxygenation and lung function [86, 87]. In a recent pilot study looking at the effects of SCUBA diving on veterans, a large reductions in post-traumatic stress disorder (PTSD) symptoms were observed [88], with pressure ranges from 1.3 to 1.5 ATA with Nitrox (32-36% Oxygen/ 68-64% Nitrogen). Not only do small changes affect the cardiopulmonary system, they appear to affect the central nervous system in a manner that promotes repair to the brain.

So, if small changes in air pressure can have a measureable effect in cell behavior and human health, why would a “sham”, as described by the Wolf et al. study, be a “sham”?

Simple: It can't. REMEMBER: A "sham" is 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.

The positive outcomes of the [Wolf et al. study](#) are due to the fact that oxygen and/or pressure have a biological effect and probably why the remaining DoD/VA sponsored studies used a different control group: A sham that controlled for oxygen concentration (10.5% Oxygen at 2.0 ATA=21% Oxygen equivalent) to a very fine degree.

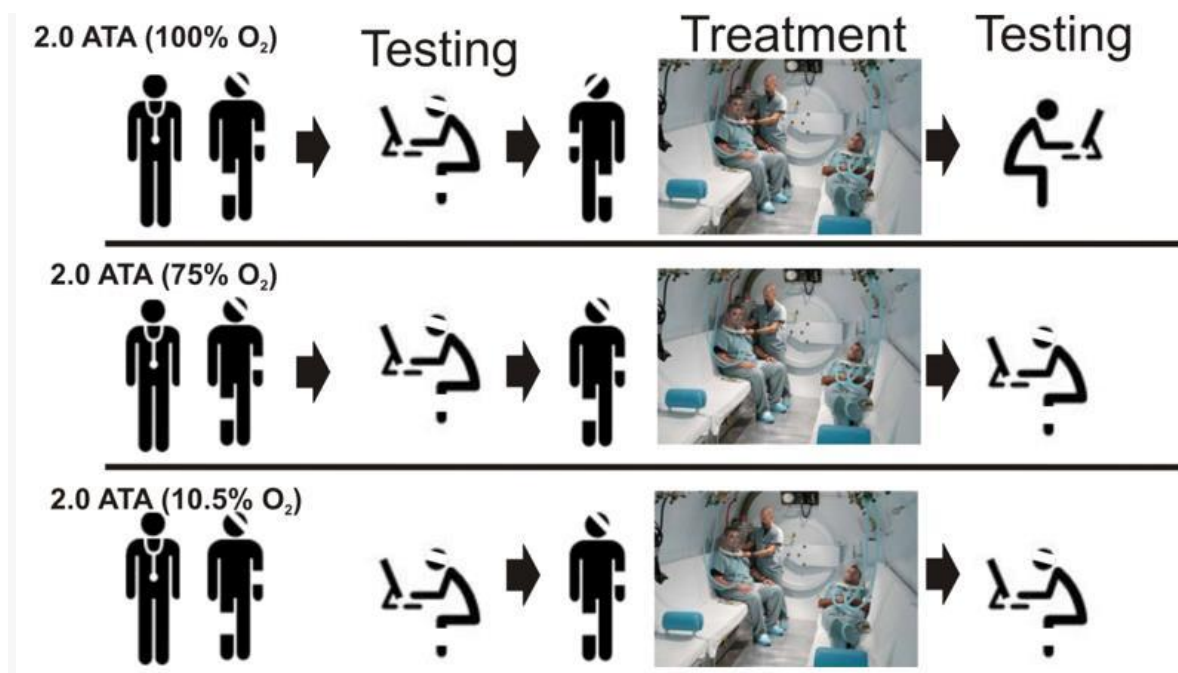
Pressure still remains to be addressed: how much effect does it have in promoting healing? This remains an under-investigated area. All these controls on variables are difficult, but necessary to address. The sham treatment was not cheap or easy to achieve, which explains why many of the previous reports of TBI treatment with HBOT do not use a placebo (do you have a spare \$1 million for the sham treatments?)

The DoD/VA Sponsored Clinical Trial

Let's take a look at the study design of the single clinical trial that was published as three independent articles. Yup, the authors got a lot of mileage out of one study.

1. Cifu, D.X., et al., The effect of hyperbaric oxygen on persistent postconcussion symptoms. *J Head Trauma Rehabil*, 2014. 29(1): p. 11-20.
2. Walker, W.C., 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*, 2013.

- Cifu, D.X., et al., Hyperbaric oxygen for blast-related postconcussion syndrome: Three-month outcomes. *Ann Neurol*, 2014. 75(2): p. 277-86.



The **single** clinical trial design is graphically represented in the figure above. Study participants were assigned into three different treatment groups (10.5 % Oxygen, 75% Oxygen and 100% Oxygen). The participants were given the exact same pressure (2.0 ATA) but given different oxygen mixtures to **simulate** different treatments. This **single** clinical trial did not attempt to replicate previous reports but approximated the process. This **single** clinical trial did not try to match what had been done in the previous report by Wolf et al. or other studies.

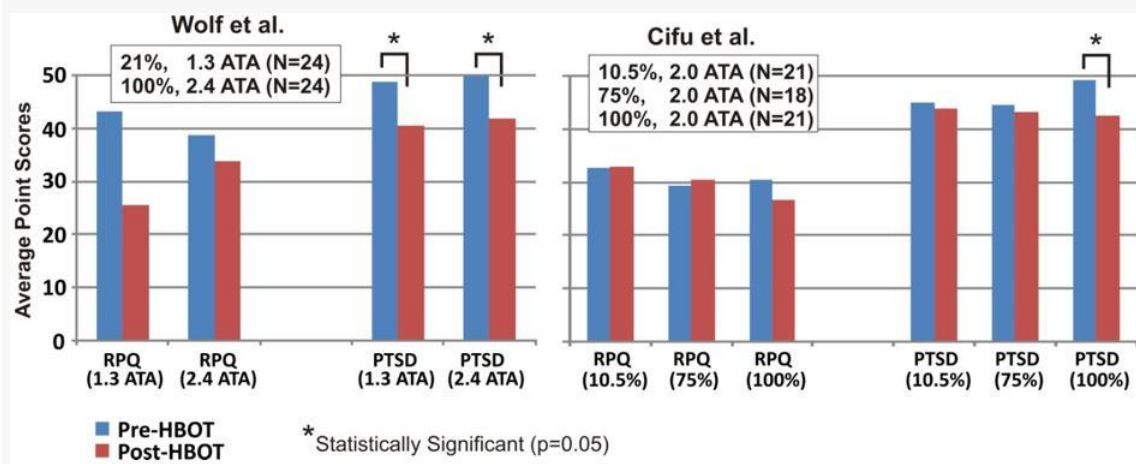
The three DoD/VA sponsored articles reported on one group of Marines (N=61(83,84); N=60(85)). These articles reported on the outcomes of a follow-up analysis (post-HBOT treatment) at 1 week, 3 months and an independent analysis of the secondary outcome measures. The two primary measures they looked at were the Rivermead post-concussion questionnaire (RPQ) and the PTSD Checklist-Military Version (PCL-M). The Walker et al. paper [89] looked at secondary outcome measures of neurocognitive performance, which we will not discuss or go into in this blog. Secondary measures are more complex and dependent on multiple neuromuscular and neurocognitive pathways.

The RPQ is a self-administered test that asks the study subject to rate symptoms associated with a TBI on a 0 to 4 point scale. The worse the symptoms severity the higher the score the participant should assign. The total maximum for points in the RPQ is 64. Higher is worse, lower is better.

The PCL-M is another self-administered test that rates PTSD symptoms on a 1-5 scale with 17 questions and has a total maximum value of 85 points. Again, higher is worse, lower is better.

In each of the articles by Cifu et al. and Walker et al., the conclusions from the authors were that there was no effect from HBOT...nothing, zero, zilch, nada. Not even the supposed placebo or Hawthorne effect showed up in any of their trials.

So, how does the Cifu study [90, 91] compare to the Wolf et al. study [82]? Please remember that all the information is taken directly from the published data and not from “unnamed sources”. We just arrived at a very different set of conclusions from the exact same data.



Just

remember conclusions and discussions are like opinions: everyone has one, but it needs to be backed-up by data. Although the Cifu et al. study concludes that the results are clinically non-significant, the aggregate PTSD scores were significant (right side), just like in the Wolf et al. study (left side).

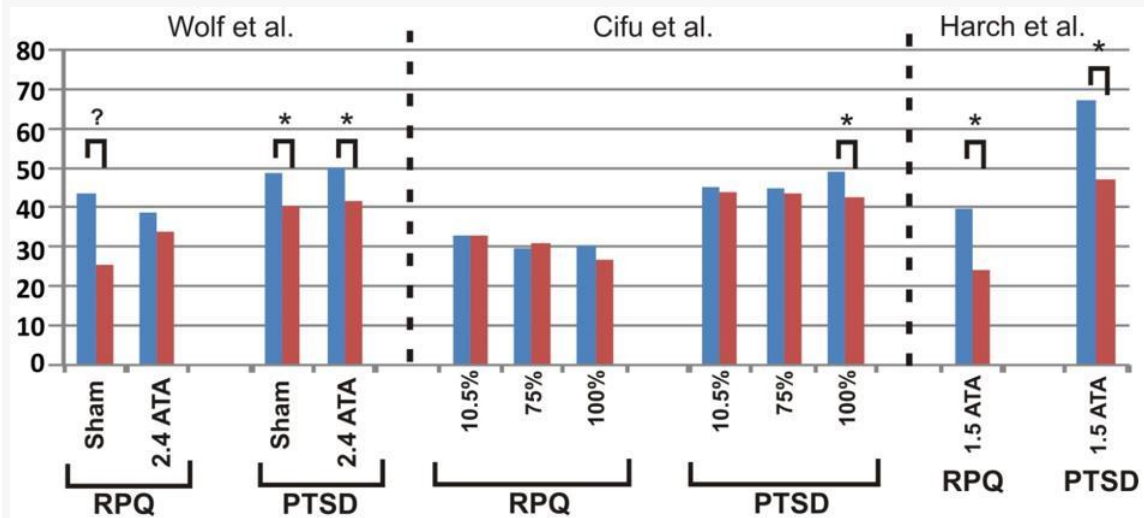
The lack of change in the other conditions for the Cifu study (75% and 100% Oxygen) could be due to insufficient number of study participants. The Wolf et al. study had 6 and 3 more study participants per group (N=24 for the “sham” and 2.4 ATA group) than the Cifu study (N=18 for the 75% oxygen and N=21 for the 100% group). Given how close the results were between both studies, the addition of 6 and 3 more study participants by the Wolf et al. study could explain the difference seen between both articles.

Another factor at play is the relatively high pressures used by both Wolf and Cifu. Around the world, scientists who have been doing research with HBOT for decades have consistently pointed out that lower pressure treatments, ideally 1.5 ATA or lower, should have greater efficacy, as higher pressures of oxygen may actually be too harsh for the injured brain. For Cifu and Wolf, the HBOT

intervention doses were at or above 2.0 ATA in pressure. The lower “sham” treatment was much closer to the ideal pressure that proponents of HBOT normally use for neurological treatments [92-95].

Now, what is really very surprising with the Wolf et al. study is the effect seen with hyperbaric air (1.3 ATA, 21% Oxygen), which critics claim is a placebo or Hawthorne effect. The effects were large (41% difference between pre and post testing on the RPQ), but they were not reported as significant in the aggregate scores, although 9 symptoms showed significant differences in the “sham” treatment group. The PTSD scores are also very close in overall effect between pre and post treatment (16% improvement in the Wolf study and 14% in the Cifu study; both statistically significant when compared between pre and post treatment.)

The changes in RPQ and PTSD score are in agreement with another published report. Harch et al. [93] treated 15 Marines with bomb-blast induced mTBIs and produced results that were in agreement with the Wolf and Cifu studies.



The conclusion of Cifu et al. that HBOT is ineffective on mTBI is not supported by the data they acquired. Although the RPQ results from Cifu et al. are different from the Wolf and Harch studies, the PTSD changes are significant and in agreement with previously published outcomes. The RPQ results of Cifu et al. are puzzling, but could be due to the small size of the study sample that was used. Obviously this is an area for research, but research can be performed while treating. Still, the overall trend between these three studies favors a clinically positive outcome with HBOT treatment.

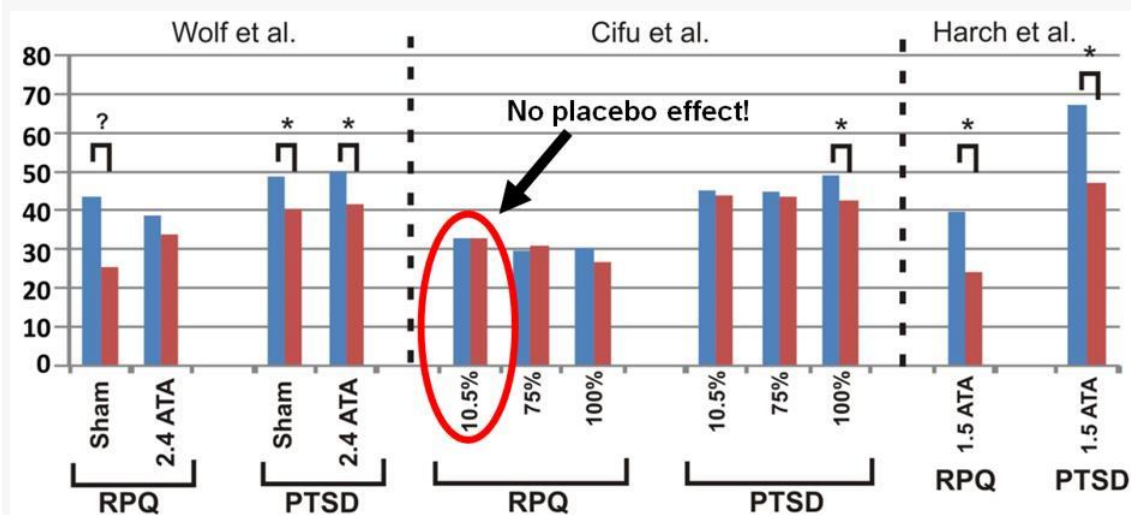
Even more intriguing is the following thought: Was the number of treatments sufficient to produce the best outcome? Thirty, 90-minute sessions were done with the Wolf et al study; forty 60-minute

sessions with the Cifu et al. and Harch et al. studies (2700 minutes vs. 2400 minutes of HBOT treatment). Would more sessions produce greater improvements?

We don't know. Only a limited number of HBOT case reports demonstrate improved outcomes with more than 40 treatments [96].

So What?! It's Still Just a Placebo!

The lack of a placebo or sham group with the majority of HBOT studies has always been held up as a major deficiency when it comes to the results obtained with neurological injuries. The placebo effect is a well recognized component of medical treatment, sometimes superseding the effects of the actual treatment. Controls are an essential component of most clinical trials, but sometimes the controls are just not feasible or too costly to set up (especially with HBOT). Placebos are not always used (cancer studies compare new drugs or procedures against standard of care all the time) and comparing pre and post measures, although not deemed the most stringent, are acceptable and valuable in medicine [97].



But the placebo objection may be a superfluous point. What was overlooked in the discussion of Cifu et al was the lack of any change in the 2.0 ATA, 10.5% Oxygen group (the 21% Oxygen equivalent). The Cifu et al study clearly demonstrated that being in the presence of a hyperbaric chamber **did not induce a placebo effect** in the study participants. The increased attention by the study technician and doctors **did not produce a Hawthorne effect** on the study participants, either (see graph above). On the contrary,

“...we found that the sham and the 1.5 ATA equivalent groups demonstrated nonsignificant [underline is mine] increase (worsening) in their raw total RPQ scores,...” (P.18) [91]

The 2.0 ATA, 10.5% Oxygen group did not produce any statistically significant changes in the RPQ or PTSD scores (placebo or nocebo), as would be expected when simulating a 21% oxygen equivalent. The sham control was a real sham control! The lack of a placebo effect and the significant effect found with the PTSD results renders the PTSD effect highly significant for the Cifu et al. study.

The concerns and criticisms leveled at the earlier HBOT studies for a lack of a sham or placebo control are greatly diminished by the Cifu et al. report. Apparently being placed inside a pressure chamber for an hour every day for 5 days does not promote the sorts of psychobiological signals that can initiate spontaneous self-healing (like a placebo should). But it does point to the fact that we are witnessing a real and powerful neurological repair/reactivation mechanism with HBOT.

How Science and Medicine Move Forward



When we talk about scientific and medical research, first and foremost we are talking about people. We all carry some sort of bias when we look at the world and try to make sense it.

Our personality, education, feelings and attitudes always alter how we perceive facts about the world. Everything we perceive around us is always filtered by the glasses we wear in our lives. Take for example the picture of the rose colored glasses. If you wore such glasses (and forgot that you were wearing them) you would come to the objective conclusion that the sky was indeed pink. Others not wearing glasses (or other colored glasses) would disagree with you and be equally valid in their objections (what a case of mass forgetfulness about glasses!)

Proponents and opponents of HBOT use different sets of filters when analyzing data and evaluating information. In many cases, researchers only see and find what they are looking for. I can safely say that as a former skeptic of the field of HBOT, I only reviewed or selected information that supported

my preconceived belief about HBOT: HBOT had limited utility and could not be used for neurological treatments. Heck, I would gloss over the data and rely on the conclusion of the author's (a very bad thing for any scientist to do. Always check over the data...always.)

It was only when I was forced to review the literature, dig through the archives and immerse myself in the decades of research publications that my bias regarding HBOT began to shift. There is an immense amount of basic biological information, of very high quality, that reports the positive and negative effects of HBOT. Decades of case reports and clinical trials point to an overall positive effect of HBOT on a wide variety of neurological conditions (stroke, TBI, PTSD). Even the reports that claim no effect, when you look them over in detail, turn out to have significantly positive results! Bias can crop up in unexpected ways. Conclusions in published reports leave a lot of room for opinions to be applied and given the patina of fact. Unfortunately, the stakes in this field are very high in terms of human cost and the promises made by a Nation to all it serving members, past and present.

Why TBI Treatment is Literally Life-And-Death



A large fraction of the current epidemic of military suicides (22+ service members a day take their lives) are more than likely due to misdiagnosed TBI and PTSD. Although the DoD and VA have spent billions (actually, \$ 9.2 billion since 2010) trying to diagnose and treat the problem, the epidemic of suicide and mental illness are larger than ever. Drug interventions are woefully inadequate, as more and more studies continue to find that pharmacological interventions are not effective in treating the varied symptoms of TBI or PTSD [98-100]. In many cases suicide of veterans have been linked through prescribed overmedication [101, 102].

On top of the military epidemic there is a large existing civilian population of TBI survivors (now ~10 million in the US alone). How many in the civilian population take their lives because the pain is just too much? How many can't work because their brain injury won't allow them to work? We don't know because we, as a society, are just starting to realize how prevalent brain injuries have become. And how many care-givers are equally and negatively affected by caring for their brain injured relatives? And what is the COST of continuing to deny a safe and effective treatment that is constantly mischaracterized?

HBOT is a safe and effective treatment with low-to-no side effects (after all, even the DOD accepted the safety of HBOT back in 2008). Access to HBOT is available within most major metropolitan centers, but the major sticking point is money. Who pays for the treatment? Those that are willing to pay for it out-of-pocket and state taxpayers picking up the tab for brain-injured service members forced back into society without sufficient care (or forced out on a Chapter 10, when it should have been treated as a medical condition).

The continued reports of studies like the DoD/VA sponsored trials allow denial of coverage and provide adequate cover for public officials to claim that more study needs to be done. As we have seen, the conclusions of the authors of the DoD/VA sponsored studies downplay the results of effectiveness. There are sufficient studies (and growing) showing a strong positive effect of HBOT in TBI. More will be forthcoming.

The cardinal rule of medicine is "First, Do No Harm". With HBOT, this rule is satisfied. Now, by denying or blocking a treatment that has proven restorative and healing effects, countless physicians and organizations, from the VA to DoD, Congress and the White House, could be accused of causing harm. Never mind how many experiments "fail" to show results (even when they actually show success). Failure to replicate a result is just that...a failure to replicate, not a negation of a treatment or other positive results. You can't prove a negative and there are many clinical trials that do show the efficacy of HBOT.

The practice of medicine and the use of HBOT should not be dependent on the collective unease of a medical profession and the dilatory nature of risk adverse politicians, but on the evidence-based results that we are seeing. Within the VA, there are hard working physicians that are trying to change the culture of inertia and implement effective treatments for TBI and PTSD, using evidence based medicine. Unfortunately, evidence-based medicine only works when we accept the evidence presented to us and not on mischaracterized conclusions of a single study (or any other study). Our veterans, our citizens and our communities deserve better than what we are currently giving them:

bad conclusions, institutions too scared to act in the interests of the people it serves and too many physicians unwilling to look at the accumulated evidence.

HBOT works for the treatment of mild-to-moderate TBI and PCS.

Treat now.

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#3: What the <#*\$&!> Is Going On With Hyperbaric Oxygen Therapy?! (Part 3)

By Xavier A. Figueroa, Ph.D.

A study was published recently under the sponsorship of the U.S. Army. This study, called HOPPS (Hyperbaric Oxygen Therapy for Persistent Post-Concussion Syndrome After Mild Traumatic Brain Injury) [1] published (Nov 17th, 2014), has received wide ranging reporting and (to my untrained eye) a media blitz for a small scale clinical trial. But, invariably, news only garners eyeballs when you sell the controversy (you can tell the story after the headline).

The headlines of the news articles reporting on the study have repeated a mischaracterization of the outcomes of HOPPS (see [here](#), [here](#), [here](#) and [here](#)), touting HBOT produces a placebo effect in mild traumatic brain injury (mTBI) study subjects ('**Treatment No Better Than Placebo for Post-concussion Symptoms**').

Sigh...

First, the authors of the study [1] concluded the following (our highlights):

“Our results support the conclusion that supplemental administration of breathing 100% oxygen at 1.5ATA(HBO procedure) or air at 1.2 ATA (sham procedure) for 60 minutes is well tolerated and improves symptoms and quality of life compared with local care management of PCS without chamber intervention.” [Bolding of the quote is ours]

But,

“It has been argued that the sham designs used in this trial and other Department of Defense studies are not inert and represent dose-ranging trials of pressurized air.[37] We recognize that a sham is not inert, and we cannot completely discount the physiological effects of minimal increases in nitrogen or oxygen from pressurized room air.”

The authors readily admit that HBOT (defined as breathing 100% Oxygen at 1.5 atmospheres absolute [ATA]) and pressurized air have an effect on mTBI study subjects, compared to **the best care that member of the active armed service can receive**. Furthermore, one of the treatment

comparators (the pressurized air control) might actually not be as good a control as they had thought (the pressurized air “sham”).

So, I was a bit taken aback when I read the following sentences in the discussion and conclusion sections,

“However, we observed no difference between HBO and sham. We postulate that improvement in the chamber intervention groups was due to placebo effects or the potential benefit of daily interactions with the study staff....Taken with results from other concurrent investigations, our study does not support phase 3 trials of HBO for the treatment of PCS at this time.”

Now, authors can conclude anything they want with their results and if the results leave room for interpretation, well, you have to give it your best shot at interpreting.

My problem with the discussion and conclusion are the following:

1. The treatment arms (pressurized air and HBOT) both showed superior outcomes in the primary measures they used (See Figure 1). Not only superior, but clinically and statistically significant than the best treatment the US Army can provide their wounded troops.
2. The recognition that one of the supposed controls was not a control.
3. The fact that two other DoD/VA sponsored studies recruiting wounded active duty members and one civilian-funded study on Marine veterans showed improvements in the same primary outcomes (symptoms for TBI and PTSD; Figure 1). That’s a total of 4 phase 1 clinical studies that showed improvements in at least 1 primary outcome and secondary outcomes.
4. At least 2 phase 1 studies in a civilian population (Table 1) that support the effects of HBOT on symptoms and cognitive performance of study subjects.
5. Concluding that (in essence): There is nothing of importance to see here. Move along. We recommend that no more research with HBOT be done for TBI/PCS.

Ordinarily, this would be a snoozer.

Unfortunately, the stakes are very high for the military service members that live with mTBI/PCS or have a misdiagnosis of PTSD [2] (see our previous post [here](#)). At a minimum, 22+ service members commit suicide [3] per day, mental health issues are presumed to be the primary drivers of the suicide (PTSD and TBI). The Institute of Medicine of the National Academy of Science concluded that the DoD and VA have spent \$9.2 billion attempting to deal with PTSD [4], but unable to stop the suicide epidemic (this study briefly mentions HBOT as a potential treatment option (p. 263) for TBI, but makes no conclusions or recommendations regarding its use for PTSD).

This is a bit of a poser for physicians. Currently, there are no phase III clinical trials that have tested the efficacy of TBI/PCS and PTSD treatments that are currently in use by VA and DoD medical. Yet, the routine prescription of drugs and therapies occurs daily. So, if a doctor wants to try HBOT for his/her patients within the Armed Services, they have to move Heaven and Earth to get the treatment for their patients. This may include getting creative in how their patients get treatment, including begging civilian groups to sponsor treatment ...but that is another story entirely.

This directly affects the civilian health care space, when it comes to treatment for mTBI/PCS. Medical groups, associations and insurance groups are unlikely to cover HBOT treatments for this type of neurological injury. The published reports can be used as justification for denying payment or treatment. This ensures that only those willing or able to pay (or provided *pro bono*) for treatment will receive HBOT.

Significantly, these reports make the pursuit of further research much harder. Funding agencies are unlikely to provide research money when the assumption of non-efficacy is so widely broadcast. Convincing other scientists and medical researchers that there is a case for using HBOT for neurological conditions then becomes an uphill battle.

This fight is far from over, but it should be unnecessary.

The cardinal rule in Medicine is

“First, Do No Harm.”

The second rule should be

“Work to Restore Health.”

If a treatment has few side effects (HBOT is safe and well tolerated [1,5,6,7,8,9,10,11,12,13] and good preliminary evidence for its use, the physician has the right and obligation to prescribe it. Other unproven treatments are applied regularly and covered.

But delay has costs to a society.

Veterans and active duty members will continue to take their lives.

Individual groups will try to find treatments for loved ones, without the help of those that should be aiding them.

People will lose faith and hope in the institutions that are charged with caring and protecting them.

And so it goes...

The fight goes on for brain health and healing.

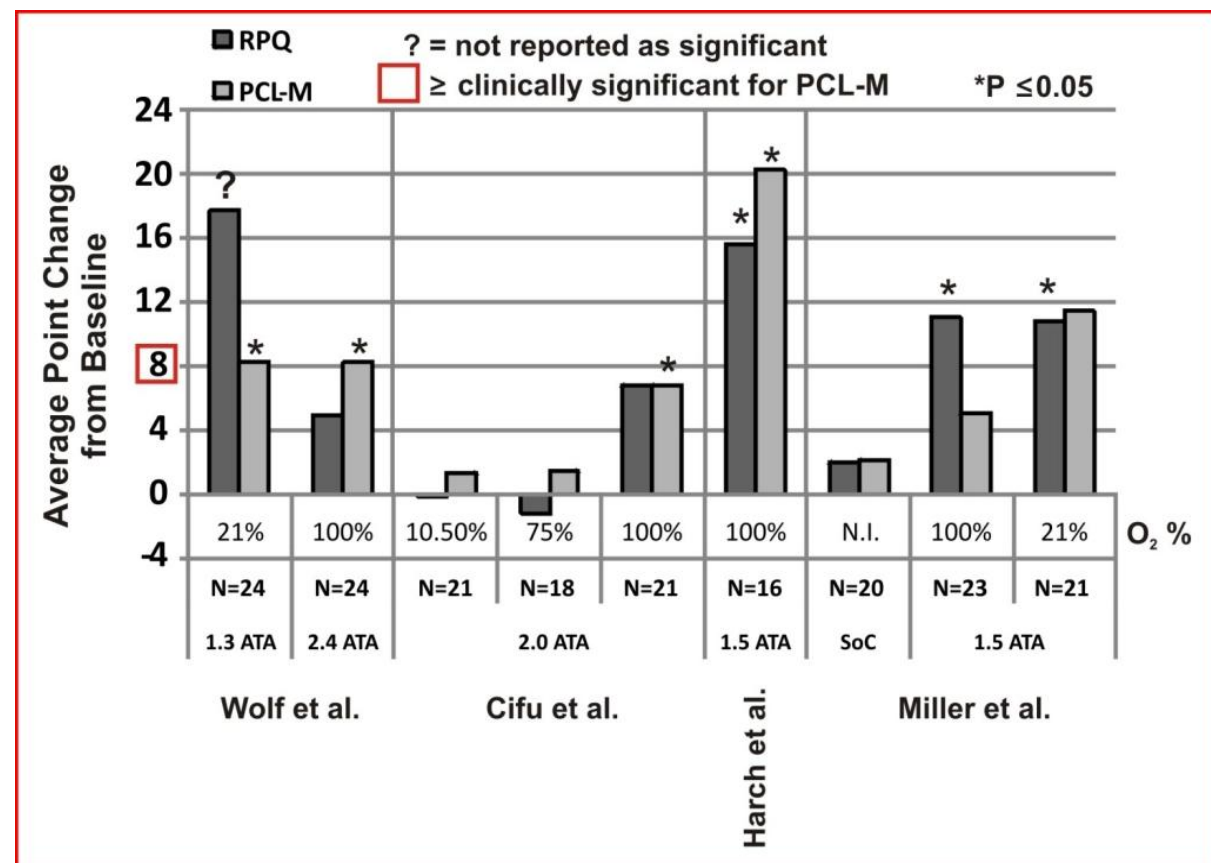


Figure 1- Primary outcomes of HBOT trials for mTBI/PCS treatment in armed service personnel and

Authors	Year	Dx	Improvement		Statistical Significance		Type of Design	# of Arms	Sham Pressure		HBOT Pressure 100% O ₂	HBOT Dives	# of Subjects (Total)	Time Since Injury
			Symptoms	Neurocog Tests	Pre/Post HBOT	Between Groups			^A (75% O ₂)	^B (10.5% O ₂) [^] (Med Air)				
Hardy et al.	2007	mTBI	Yes	Yes	Yes	N/A	Pre to Post	1	N/A	2 ATA	20/60	1	12 months	
Lin et al.	2008	mTBI	^{SOX} No/Yes	N/A	^{SOX} No/Yes	Yes	RCT w/ SoC group	2	N/A	1.5 ATA	40	22/22 (44)	> 3 months	
Wright et al.	2009	mTBI	Yes	Yes	Yes	N/A	Pre to Post	1	N/A	1.5 ATA	40	2	8 months	
Stoller et al.	2011	mTBI	Yes	Yes	Yes	N/A	Pre to Post	1	N/A	1.5 ATA	40	2	3 months/ 20 years	
Boussi-Gross et al.	2013	mTBI	Yes/No // Yes	Yes/No // Yes	Yes/No // Yes	Yes // No	Cross over	2	N/A	1.5 ATA	40	32/24 // 24 (56)	~34.6 months / ~31.7 months	

Table 1 – Studies using HBOT in mTBI/PCS reports and clinical trials.

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#4: Veterans Have Seen This Before: Memories of Vietnam?

by Xavier Figueroa

On September 21, 2013 USA Today published an article titled, “**Hyperbaric chamber treatments did not help with mild TBI**”. The article started with a picture of Michael Jackson in a hyperbaric chamber. I was unsure as to the purpose of leading off with this image: To show someone using a hyperbaric chamber or ridiculing the users of hyperbaric medicine?



Mr. Jackson had to

undergo hyperbaric oxygen therapy (HBOT) to help heal second degree burns he received after an accident during a Pepsi commercial he was filming (images taken from the CBS News website and the Daily Mail). Jackson sued Pepsi Co and settled out of court for \$1.5 million. The settlement was donated to the Brotman Medical Center in Culver City, California, where Jackson received treatment for his burns. The money donated by Jackson, was used for treating burn victims. The burn ward at the hospital was later named the “Michael Jackson Burn Center”.



The pictures taken of Michael Jackson inside a hyperbaric chamber is often used to highlight his supposed eccentricities. In actuality, the medically sound procedure was used to help him heal his burned skin (see <http://membership.uhms.org/?page=Indications>). The images of him inside a hyperbaric

chamber were taken as part of a tour he was doing for the facility he helped to upgrade with his donation. He never owned or used a hyperbaric chamber for non-medical treatments. So, I have to wonder why this particular image was used, what was the intended message?

Here is the link to the USA Today article if you are interested in reading it: <http://www.usatoday.com/story/nation/2013/09/21/tbi-treatment-research-military-hyperbaric-oxygen-chamber/2842695/#!>. It's short and to the point. It was written in response to important clinical studies looking at the effects of HBOT on the treatment of mild traumatic brain injury (mTBI) symptoms in active duty personnel.

The tone of the USA Today article suggests that HBOT is peddled as a cure-all, snake oil gimmick, perpetuating a myth that has been around medicine for several decades. The tone of the article highlights the idea that hyperbaric oxygen therapy (HBOT) did not help with TBI treatment in active duty personnel on the review of the results from the DoD funded study. Reading the introduction and discussion sections of the article by Wolf et al (*The effect of hyperbaric oxygen on symptoms following mild traumatic brain injury. J Neurotrauma 2012; 29: 2606-12*) you would come to the conclusion that HBOT did not have any effect on the treated service members, when the opposite was true. Their summary conclusion in the report admits "Symptom improvement was observed with an average 30% reduction in symptoms." This was only the average after 40 treatments. No drug or therapy currently being tested comes close to these results.

It is interesting that the authors focused on the negative results of the study without highlighting the positive outcomes (which were very positive). In most scientific and medical publications, researchers focus on the positive outcomes of the study. Negative results are very rarely published or discussed, yet with the DoD studies the negative outcomes were front and center. This is highly unusual.

Context for the Research: Diagnose & Adios

Currently, the Department of Defense (DoD) is facing a crisis. They have a lot of people suffering from traumatic brain injuries (TBIs) in active duty personnel. And by a lot, I mean 450,000 active duty service members with long-term symptoms and cognitive problems from deployments during the year 2000 up to now. This is a problem, as many of these folks cannot handle the active duty work load and require medical attention. They face the prospect of being medicated for life, medically discharged and not being able to hold down a job after they leave. The Veterans Administration has a 3-9 month backlog of cases requesting psychiatric support and if you are discharged from the service without an 'honorable' citation, you cannot access benefits from the GI

Bill and VA. Many of these individuals are being discharged for behavioral issues and their TBI or PTSD diagnoses are not considered mitigating factors, even when medical personnel step in to advise commanders of the facts ([see here](#)).

These post-TBI conditions are usually referred to as post-concussion syndrome (PCS) or persistent post-concussion syndrome (PPCS) with different levels of severity. Anyway, there is no recognized effective treatment to reverse the symptoms and cognitive deficits, only to adapt to a “new normal” in life expectations. Estimates put the total TBI load of PCS/PPCS veterans to be around 800,000. This, of course, includes the legacy of Vietnam, which had (by some estimates) an equally large number of TBIs from IEDs, bomb-blasts, service related head injuries and non-combat related injuries. Let’s not forget the Agent Orange fight that many veteran service members had with the DoD and the Veterans Administration ([see here for the back story](#)).

Living with a TBI is a huge ongoing cost for federal, state and local governments in the U.S. Some estimates put the drug costs for symptoms management at \$32,000 per Veteran. This does not count the indirect costs of unemployment, disability and ongoing care costs, coupled to the loss of tax revenue from an individual not capable of working. Each untreated TBI is a double or triple whammy to budgets at all levels of the economy and government.

None of the drugs prescribed treat the underlying TBI. They are used in an “off-label” manner for symptom management. “Off-label” means that none of the drugs that are used to manage the symptoms of a TBI are approved by the FDA.

Here’s an example: anti-depressants are prescribed for major depressive disorders (MDD), not for depression secondary to or derived from a TBI. That is a key difference that must be made. People with a TBI have depression symptoms, but the cause of the symptoms is very different from an MDD case. The effects for certain anti-depressants are not known with people that have a TBI.

In some cases, the use of anti-depressant may have produced the opposite effect and promoted suicides ([click here](#)). Hence the title of this section: diagnose and adios (literal Spanish translation that means in God’s hands). Doctors do not have a lot of recognized options for treatments, so if you are diagnosed with a TBI, at least you know you are suffering from something. Adios, sorry we can’t do anymore. Here are some pills that may or may not work.

Experimental Treatments

So, this brings us back to the DoD sponsored studies. Two studies have been published looking at the effect of HBOT on TBI on the mild-moderate classification (Wolf et al. 2012 (1); Cifu et al., 2013

(2)). These studies look at different pressures of hyperbaric oxygen therapy, but they measure the same outcomes. It is thought that different pressures of oxygen act like different dosages of a drug. Trying to find the right “dose” for TBI treatment is an ongoing debate in hyperbaric medicine. A substantial proportion of the medical community in the United States believes that the recovery from a TBI that is seen with HBOT is a [placebo effect](#), hence rendering the HBOT treatment a very expensive sugar pill.

But how do you make a placebo for oxygen? A placebo is defined as "a substance or procedure... that is objectively without specific activity for the condition being treated" (3). Oxygen is essential for all metabolic activities in the body. By definition, oxygen cannot be a placebo as it is required for any healing process to take place. So, how do you go about testing oxygen in a placebo controlled trial for HBOT?

Both studies looked at the effects of the most common symptoms associated with a TBI (using a questionnaire called the Rivermead Post-concussion Questionnaire, RPQ). Both studies treated for 40 sessions per study subjects (for 60 minutes) at different pressures (**Study 1**– 2.4 ATA and 1.3 ATA; **Study 2**– 1.5 ATA, 2.0 ATA and a sham treatment). Both studies showed statistically significant improvement from pre- and post-HBOT treatment looking at the RPQ measures, but not when comparing them between groups (that is, comparing the 2.4 ATA group against the supposed sham or placebo control of 1.3 ATA).

The authors, in both studies, chose to diminish the positive outcomes from these studies and declare that HBOT does not work for the treatment of mild-moderate TBI. Also, these studies are not completed. There are more pieces that need to be published. The DoD reports are preliminary and should be taken that way. Yet, the media pronouncements (as highlighted by the USA Today Article) and PR from DoD are crafting the message: the results are in, nothing to see here.

Now, the most common complaint that critics of HBOT for TBI point to is that the studies that show the positive effects of HBOT on TBI patients do not have a placebo control. Well, true. But those studies recruited people that had been living with their TBI conditions for 3 or more years...clearly indicating that there was very little chance of spontaneous recovery. Yet, the results are criticized because a control group is missing. Any positive results must be due to a placebo effect and the placebo effect must be very strong (to account for the permanent improvements in study participants) when hyperbaric chambers are utilized. Again, oxygen cannot be used as a placebo...and removing oxygen from a treatment would kill the study subject. How do you actually perform a study?

The placebo controlled, double-blind and randomized studies are referred as the gold standard for determining the efficacy of a drug, compound or therapy. But other study designs are just as good depending on what you are testing. When placebos are not easily defined, cross-over studies can provide essential information regarding the efficacy of a treatment. A crossover study is a longitudinal study in which subjects receive a sequence of different treatments (or exposures).

Randomized, controlled crossover experiments are normal in health care clinical trials. In a randomized clinical trial, the subjects are randomly assigned to different arms of the study which receive different treatments. When the randomized clinical trial is a repeated measures design, the same measures are collected multiple times for each subject. A crossover clinical trial is a repeated measures design in which each patient is randomly assigned to a sequence of treatments (of which one "treatment" may be a standard treatment or a placebo)

(http://en.wikipedia.org/wiki/Crossover_study). Some trials with HBOT have followed this approach and come to conclusions that are opposite of the DoD studies.

New Evidence

In November of 2013, an Israeli group from Assaf Harofeh Medical Center looked at the ability of HBOT to reverse the symptoms and cognitive deficits of TBI sufferers in the post-concussive phase of the injury {Boussi-Gross, 2013 #14041}. Their study looked at 1.5 ATA treatments and compared a baseline group, which was then crossed-over into an active treatment group. They found that there was a significant improvement in symptoms and cognitive performance when compared to baseline and between group measures.

More importantly, it calls into question the results of the DoD studies. It also implies that HBOT can be used as a treatment for TBI and potentially post-traumatic stress disorder (PTSD) secondary to a TBI. Hopefully the DoD will begin to offer this treatment protocol to all personnel diagnosed with a TBI and help halt the ongoing suicide and attempted suicide epidemic within the Armed Services (24 and 45 per day, respectively). HBOT is a tool that more medical providers, especially neurologists and psychiatrist should become more familiar with.

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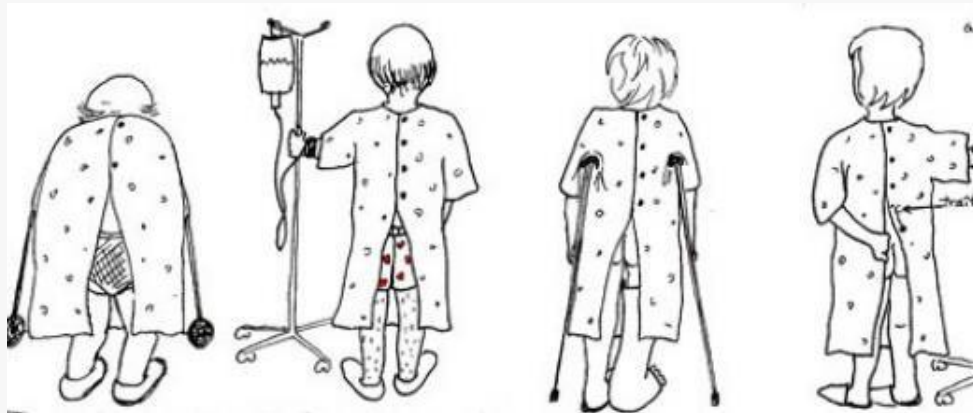
Passing Gas: A brief explanation of hyperbaric oxygen therapy

by Xavier Figueroa

Let's make one thing clear: **Hyperbaric oxygen therapy is nothing like a rectal or prostate exam!**

Don't get me wrong; having a finger or a tube shunted up your rear end is useful for detection and diagnosis of cancer but – let's face it – both exams are <ahem> intrusive.

Fortunately, getting hyperbaric oxygen therapy (HBOT, HOT or HBO₂T; lots of acronyms for this therapy) is much less intrusive, a lot more relaxing and it keeps your dignity mostly intact (unless you are wearing a hospital gown... **immediate** destruction of dignity! *Image below from Sous La Blouse*).



HBOT adds up to breathing 100% oxygen at a pressure greater than what you experience at sea level (sea level = 1 ATA) while inside an air tight container. If you live in a mountain region, you are breathing air at a pressure below sea level, about 0.95 ATA (if you need more information about atmospheric pressure and such, please go to this Wikipedia page: http://en.wikipedia.org/wiki/Atmospheric_pressure). For the majority of accepted treatments, pressures in the range of 2.4-2.8 ATA are normal in HBOT, but new treatment protocols in the 1.5 to 2.0 ATA are being tested for neurological injuries (more on that later).

All medical grade chambers are either made out of steel or spun acrylic shells and come in two flavors. One flavor is a mono-place chamber (picture on left). This single-patient chamber is exactly what it sounds like: It fits one person. The other flavor is a multi-place chamber and – you guessed it – can accommodate more than one person (middle image is the interior, right image is the exterior of a multi-patient chamber).



Images are from: <http://tinyurl.com/kgefwt6>

So, why do people go into hyperbaric chambers?

Well, the only time most people will experience the thrill of going into a chamber in the United States (and have insurance pay for the ride) is when they have suffered some form of injury or infection.

Most common uses of HBOT are listed below:

1. Air or Gas Embolism
2. Wounds
3. Carbon Monoxide Poisoning
4. Severe Anemia
5. Intracranial Abscess
6. Clostridial Myositis (Gas Gangrene)
7. Necrotizing Soft Tissue Infections
8. Crush Injury, Compartment Syndrome
9. Osteomyelitis (Refractory)
10. Decompression Sickness
11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
12. Central Retinal Artery Occlusion
13. Enhancement of Healing In Selected Problem
14. Compromised Grafts and Flaps
15. Acute Thermal Burn Injury

Now, all this list means is that a medical review group (in the case of HBOT, it is the Undersea Hyperbaric Medical Society) has reviewed the evidence for or against the use of HBOT for the listed conditions and said “Yup, we think that this does work for this type of injury/disease”. A group of people, well trained, educated and experienced practitioners of the art of HBOT agreed that there was enough medical evidence to give it the UHMS seal of approval. In some cases, the conditions on the approved list were “grandfathered” in due to the years of clinical experience and consensus by medical peers. In other countries, the list of approved indications is much larger and generally paid for by insurance.

Now, in the U.S., the FDA grants approval for indications, but it is a doctor’s right and responsibility to practice his or her art to the best of their ability. This means that they can prescribe treatments that are considered “off-label”. This means that they can prescribe drugs or treatments that are approved for one condition (e.g. – blue pill for erectile dysfunction) for a completely different unapproved condition (e.g. – blue pill for glaucoma). The medical branch of the Department of Defense works in the same way when treating armed service personnel; they routinely prescribe drugs and treatments to manage condition like traumatic brain injury with drugs that are not approved for TBI treatment. HBOT medicine works in much the same way, with physicians prescribing it use for a condition that has not been formally approved yet.

A newly added indication (an indication is an approved treatment condition) is the use of HBOT for the treatment of idiopathic sudden sensorineural hearing-loss (ISSHL). ISSHL is related to tinnitus (another potential injury that has some clinical evidence of being treated by HBOT), but is an acute loss-of-hearing capacity. This new (just approved 2012) indication serves as an important example of how treatments are approved or validated here in the United States. It took many years, starting with anecdotal evidence from people suffering ISSHL and recovering after HBOT treatments to start the ball rolling for this new indication. After some controlled studies were done over 10 years, the medical community recognized HBOT as an effective treatment for ISSHL.

Still, it doesn’t guarantee whether or not a health insurance company will pay for the treatment, as many doctors and patients know from experience. That is the great limiting factor for HBO: Who pays for the therapy? Even though there are numerous cases of conditions being treated by HBOT and improving (like autism or stroke; [click here and here](#)), it sometimes requires legal action in order for insurance to cover treatment. And resorting to legal action in order to cover your medical bills is definitely like a prostate or rectal exam... deeply uncomfortable and it diminishes your dignity.



How Does Hyperbaric Oxygen Work?

OK... do you know how to make carbonated or soda water? You fill a bottle with water, connect the filled bottle to a high-pressure carbon dioxide cylinder and open the valve. The high pressure from the CO₂ cylinder forces gas into the bottle and the high pressure dissolves the CO₂ into the water. Voilà! Soda water!

Many companies manufacture machines that do just that (such as SodaStream). Carbonating water is similar to how HBOT works, although there is a lot more safety equipment and NO carbon dioxide! When you deliver pressurized gas into water, the gas dissolves into the water! When you pressurize oxygen into the body, you are dissolving oxygen into the water of the body (and also into the fat and muscle, too). Nitrogen is not included, as it can form bubble more easily when you undergo decompression and it is oxygen that promotes the healing effects that have been observed and reported. Oxygen, once dissolved into water, tends to stay dissolved. Also, the body is always looking for oxygen for the cells. When oxygen is dissolved in the plasma of blood (the water portion of blood), cells gobble it up almost immediately.

This excess of oxygen (as well as the pressure), induces a number of changes in gene expression (genes are turned on that promote survival and repair), new blood vessel grow (angiogenesis) in areas that are low in oxygen content. HBOT has the added bonus of stimulating the release of stem cells from bone marrow (which have been shown to promote healing), promotes mitochondrial repair and improved function (mitochondria provide the power for cells), induces a state of analgesia (pain sensation diminishes), promotes wound repair and can induces the growth of brain cells (neurogenesis). To see all the benefits and the literature, please go to this short article ([HBOT Facts](#)).

HBOT and More

HBOT is only one tool that the Brain Health & Healing Foundation is testing to treat brain injuries and diseases. There are several other technologies and treatments that have the promise to restore lost function and halt disease progression in neurological conditions. Unfortunately, the focus of the majority of research in neurological conditions is to pursue pharmacological and genetic engineering approaches. Very few research programs look to improve or support the bodies' ability to heal. We plan to change that... with no loss of dignity or hospital gowns.