The 900 lb Gorilla in Hyperbaric Medicine

By Xavier A. Figueroa, Ph.D.

Boy, did I call it on my November, 2014 blog post.

I just recently heard back from contacts within the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH). The DoD/VA and Army studies (which wrongly concluded that HBOT did not work) [1-4] have created a very high barrier for funding hyperbaric oxygen therapy (HBOT) research that involved neurological injuries. This is bad news, as researchers who are trying to understand the applicability of HBOT must counter a bias of inactivity coming from three huge federal agencies. As I stated in November:

> *"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."*

The DoD/VA and Army study results demonstrate that HBOT is an effective treatment tool to help reverse the symptoms and cognitive deficits from a TBI. The DoD/VA and Army studies are comparing doses of oxygen (21%, 75% and 100%) that are biologically active and therapeutic for the treatment of TBI/PCS. When you compare an active dose to an active dose, you will never see a difference in effect; they are both working.

All three study groups (Wolf et al., Cifu et al. and Miller et al.) produced well funded, sham controlled double blind and randomized clinical trials (RCTs). This level of adherence to the gold standard for clinical trial design gives the results of these three clinical trials an academic heft that is hard to ignore. But these trials suffered from a weaknesses in design of the trials: The "sham" interventions used in the three trials (DoD/VA, Army) [1-4]were not shams, but different doses of an active ingredient (or ingredients). The design flaw in each study invalidates the conclusions of a placebo effect, supporting the alternate conclusion: HBOT and HBAT are both neuroprotective and neurorestorative. The controls that the study authors used were defined as shams, but all the evidence points to pressurized air (21% O2) having biological and therapeutic activity.

Creating A Sham "Out of Thin Air"

The currently used sham intervention in hyperbaric medicine (1.2 to 1.5 atmospheres absolute [**ATA**], medical grade air: 21%O_2/ 79% N_2) was developed in order for study subjects to believe that they are receiving a full hyperbaric treatment (the sensation of pressure in the middle ear) [5]. One major study by Rainolds et al. [5] was solely focused on verifying that pressures at or above 1.2 ATA would fool

trained divers into thinking they were undergoing a standard treatment at a pressure of 2.25 ATA. The reasoning behind the Rainolds et al. study was as follows: If you could fool trained divers, you should be able to fool people with no dive experience. The study did not look to see if there was a biological response to either treatment pressure.

Now, the majority of treatments that are usually performed in the United States use pressures in the range of 2.4 to 2.8 ATA (rarely as low as 2.0 ATA) with time varying from 60, 90 or 120 minutes. The pressure and time in HBOT is dependent on the wound or injury that is being treated. The majority of physicians normally do not apply treatment pressures that go below 2.0 ATA. For all they know (or have been taught), there is no therapeutic activity of oxygen (assumed to be at 21% O2) or hyperbaric oxygen (at 95-100% O2) below 2.0 ATA.

There is evidence that tissues (like skin) are not sensitive to low concentration oxygen. Shams (air at 2.5 ATA) do not report the same effect as 100% O2 (≥ 2.4 ATA) for wound closure [6]. Different organs and tissues may be more or less sensitive to oxygen enriched exposures. The brain and the lungs cannot tolerate prolonged exposure to 100% O2 at pressures greater than 2.0 ATA or at 1.0 ATA, respectively [7, 8]. As a toxicologist this tells me that these tissues are very sensitive and reactive to changes in O2 and may explain why we see therapeutic changes with low dose HBOT and hyperbaric air. No direct study on the minimum level of oxygen + pressure has ever been undertaken to establish a true sham (no biological or therapeutic activity) for the central nervous system or other organs. This remains a major obstacle for acceptance and development of true placebo/sham controlled trials. Not even the governing bodies in hyperbaric medicine have looked into it.

The Underwater and Hyperbaric Medicine Society (UHMS) committee is a body of physicians, clinician, researchers that set policy and guidelines in hyperbaric medicine. The UHMS committee was not tasked to determine what minimum level of oxygen elicits a clinically relevant exposure in the central nervous system. The UHMS committee only looked at the evidence for the indications listed for review [9] and presented an opinion on the medical definition that the UHMS would accept as a hyperbaric oxygen treatment. The review focused in treatments that are normally applied at pressures ≥ 2.4 ATA and did not report on the effects that have been reported at pressure < 2.4 ATA (like 1.5 or 2.0 ATA for brain injuries) or with variations in gas concentration (O2 concentration < 100%) for neurological injuries or disorders.

The DoD/VA and Army studies took the UHMS committee definition of a hyperbaric treatment at face value and made the assumption that pressurized air would not be therapeutic. No in-depth or rigorous review of the hyperbaric medical or research literature was undertaken by the DoD/VA or Army sponsored study groups to ensure that the chosen pressure/oxygen mixture was a true sham. The DoD/VA/Army research groups assumed that the "sham" treatments chosen as comparators would not elicit a therapeutic response in the brain. Pressurized air (21% to 75% oxygen), even at doses considered low or ineffective by hyperbaric physicians (1.1 to 1.5 ATA; O2 concentration < 100%), can produce a therapeutic and protective effect on many organs and tissues.

At this point I would bore you with an exhaustive and detailed description of the evidence for the biological activity of pressurized air in cell culture, animal models and human trials [10-21] [22-26], but I won't. The references are there for you to look up, if you got your nerd on for it. Suffice it to say, the evidence is clear that pressurized air is active and therapeutic on the central nervous system. People

may argue against it, but the reported scientific evidence in the English language is quite clear: pressurized air is therapeutic. Any argument against is made in ignorance of published fact. Pressurized air (21% O2) is not a sham treatment for central nervous system injuries.

Results from TBI/PCS Studies Using HBOT and HBAT

The DoD/VA and Army sponsored studies uniformly conclude that exposure to HBOT is a placebo effect. On the other hand, two independent studies in the US and Israel based their clinical trial design on the knowledge that utilizing compressed air as a control comparator was not supported by published evidence [26, 27]. The DoD/VA and Army trial conclusions ran counter to those reported by the two civilian studies. Fortunately, four of these studies [2-4, 27, 28] used the same measures for primary and secondary end-points: TBI symptoms scores and the PTSD Checklist-Military (PCL-M). The reported results (and not the interpretation of the results by the authors) of the TBI and PCL-M measures reveal critical facts in support for therapeutic action of HBOT and HBAT. With only one exception, all members exposed to HBOT or HBAT improved significantly from their baseline scores (Figure 2, left) in TBI and PTSD measures. The stars on top of the bars indicate statistically significant changes in scores. The HOPPS trial [28] was the only study sponsored by the Federal government to include a standard of care (SoC) group, demonstrating the therapeutic effects in both HBOT and HBAT. Figure 2 displays the results arranged in two ways: 1) By corresponding authors (left) and 2) By increasing amounts of dissolved oxygen in blood (Figure 2, right). Both the TBI and PCL-M symptom scores can be fitted to a 6

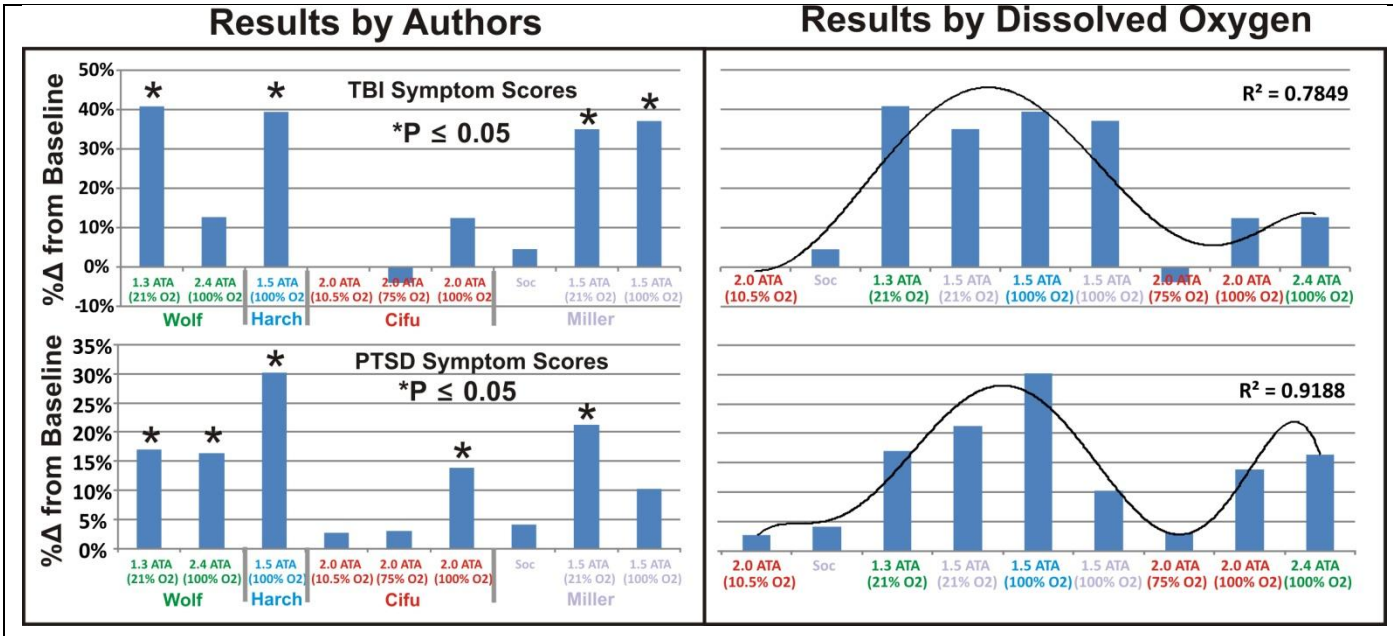

Figure 2 – Comparison of TBI symptoms and PCL-M results from four studies. Left, the total % change from baseline for TBI symptoms (top) and PCL-M measures (bottom). All studies report at least one statistically significant improvement in both TBI and PCL-M measures. Right, total % change from baseline score for TBI and PCL-M measures arranged by increasing dissolved oxygen (left to right). Both TBI symptoms scores (top) and PCL-M scores (bottom) are best fitted by a 6 order polynomial (R^2 score in graph).

order polynomial line (fancy talk for: an equation can account for the shape of the curve). On the TBI and PCL-M scores (top and bottom, right graphs) the lines describe a therapeutic dose response curve. For the TBI and PCL-M scores, the peak of activity appears to be between 1.3 ATA (air) and 1.5 ATA (oxygen). Increasing pressure above 2.0 ATA (while maintaining 75%-100% O2) appears to reduce efficacy, more than likely due to increased toxic effects of oxygen on the brain. It is highly unlikely that this could be due to a placebo effect, since all the participants did not know the dose they were receiving in these studies. The know effects of a higher placebo response rate (in pain management studies) when an injection over a pill is administered [29] does not correspond in these cases. With only one exception [27], all study participants were blind to treatment pressures. There was no foreknowledge of relative "strength" of the chamber treatments.

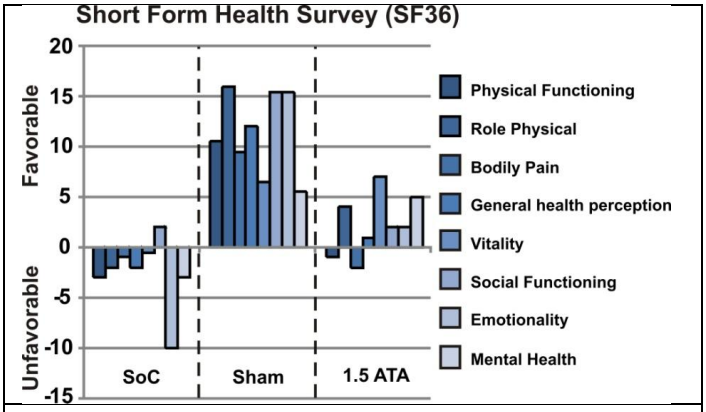

Figure 3 – Results of the SF36 survey in the HOPPS trial.

Furthermore, the HOPPS study demonstrates a partial dose response in one of the measures they used. The Short Form Health Survey (SF36) is a quality-of-life assessment tool that measures eight areas, ranging from physical function to emotion well-being (Figure 3). In the results of the SF36, the "sham" (1.5 ATA, 21% O2) demonstrates greater improvement in all measures when compared to the higher dose arm (1.5 ATA, 100% O2).

Summary: The TBI/PCS studies that used HBAT as a "sham" were in reality a dose comparison study. The DoD/VA and Army sponsored studies demonstrated that HBAT is a safe and effective dose and HBOT is an effective intervention to treat the symptoms and cognitive impairment of a TBI/PCS. Higher treatment pressures appear to be less effective, probably due to increased toxic effects on the central nervous system. HBAT and HBOT elicit therapeutic effects on the brains of TBI/PCS victims.

Conclusion

Given the previous publications reporting the biological and therapeutic effects of HBOT & HBAT, the conclusions of many of the reported negative results in various HBOT studies for neurological injuries must be reassessed [23-25] [2-4, 28]. The dose response profile that emerges from four studies on HBOT and HBAT for TBI/PCS treatment must give clinical researchers pause to reconsider current and past results in the literature. The safety of HBOT (or HBAT) is not at issue and higher pressure treatments are routinely applied for wounds, tissue necrosis and recalcitrant infections of bone [9] without increased morbidity or mortality due to HBOT. In a retrospective safety study of a single site that treated 8, 100 patients [30] in a 22 year period, non-fatal incidents occurred in less than 1% of patients, with zero fatalities. A 73 year review of hyperbaric medicine world-wide, revealed that fatal accidents or explosions have not occurred in North America [31] up to 2008, making it one of the safest clinical procedures in medicine. HBOT and HBAT are important tools to help repair damage to the brain and should be a standard treatment in support of a functional medicine approach to recovery and

health maintenance. Veterans and active duty members are killing themselves due to TBI and PTSD. HBOT can provide a much needed intervention to improve symptoms and begin healing the brain. HBOT is not a silver bullet, but when managed in an integrative and functional medicine approach (diet, hormone rebalancing, heavy metal chelation, meditation, therapy) you will restore a broken brain and body into a functional brain and body.

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