Evidence For Use Of Hyperbaric Oxygen Therapy For Acute Traumatic Brain Injury

Traumatic brain injury (TBI) affects over 1.6 million United States residents annually and a far greater number internationally (Ghajar). Over 50,000 of these individuals will die from their brain injury and greater than 80,000 will have permanent severe neurological disability (Ghajar). Since the development of modern emergency medical system (EMS) management of acute trauma no therapeutic modality has further reduced the mortality of traumatic brain injury. The data below will show that the only modality in the history of science and medicine with a scientifically proven reduction in mortality in acute severe traumatic brain injury is timely low-pressure hyperbaric oxygen therapy (HBOT). Some of this data also suggests a benefit for functional improvement.
Any discussion of the effect of HBOT on a medical condition should be based on the concept of drug dosage. A comprehensive definition of HBOT as a drug is necessary: HBOT is the use of greater than ambient atmospheric pressure oxygen as a drug to treat basic pathophysiologic processes/states and their diseases (Harch, Jain). The dose of HBOT is a function of the fractional percentage of oxygen, rapidity of pressurization and depressurization, depth of pressurization, length of time at depth, frequency of treatments, presence or absence and duration of air breaks and surface intervals, number of treatments, and time of intervention in the natural history of the disease, which identifies the pathological targets. The data in this paper will be discussed and evaluated in terms of dosing and will emphasize the absolute pressure, time at depth, frequency and number of treatments, and time of intervention. The medical literature will be reviewed to first answer the question of efficacy of HBOT on the underlying pathology, pathophysiology, and outcomes of acute TBI in animals and second to see if this efficacy is duplicated and reinforced by the human clinical literature.

TBI is a diffuse cerebral insult characterized by primary mechanical disruption of tissue (Peerless), (Strich), (Adams) and secondary injury from ischemia (Bouma), hypoxia(Adams), (van den Brink), (Zhi), edema (Adams), (Schoettle), (Bullock), vasospasm (Martin), (Zurynski), neurochemicals (McIntosh), (Hovda),and reperfusion injury (Zhuang), (Schoettle). A review of the medical literature shows that there is substantial data proving a beneficial effect of HBOT on the secondary injury processes of acute TBI. HBOT has been shown indirectly to improve ischemia and hypoxia in acute TBI by its effect on aerobic metabolism and EEG. Contreras (ref) recorded a persistent increased cerebral glucose utilization in 5 of 21 areas of brain remote from a cryogenic injury 24 hours after the fourth HBOT. Treatments began 30 minutes after the injury and continued daily at 2 ATA/90 minutes. Holbach (J. Neurol) obtained a similar result in humans with acute severe TBI (23 patients), and stroke (7 patients) a few days post injury/ictus. Measuring the glucose oxidation quotient, he found aerobic metabolism to be maximal in injured brain at 1.5 ATA. A single 10-15 minute excursion to 2.0 ATA had a toxic effect on glucose uptake and metabolism that persisted after return to room air. Holbach (6th Int. Congress) reinforced this finding by demonstrating simultaneously improved EEG and decreased regional cortical blood flow (rCBF) in a similar or the same group of acute severe TBI patients at 1.5 ATA. Upon presure increase to 2.0 or 2.5 ATA for 30 minutes EEG markedly deteriorated and rCBF

increased significantly. Some patients experienced persistence of these toxic effects upon return to room air.

HBOT also has beneficial effects on vasospasm. Yufu showed that 30 minutes after sub-arachnoid hemorrhage a single HBOT at 2.0 ATA/60 minutes reversed reductions in Na+, K+-ATPase activity and cell membrane alterations. Similarly, Kohshi documented a clinical benefit of HBOT on vasospasm in a controlled human study. He found that HBOT at 2.5 ATA/60 once or twice/day (average 10 treatments) soon after symptomatic vasospasm in post-op SAH/aneurysm patients decreased strokes and improved neurological outcome and EEG over controls.

Multiple studies have shown that HBOT reduces cerebral edema and decreases ICP. Coe used a single 3.0 ATA/120 HBOT immediately after cryogenic brain injury in rats to improve neuronal destruction, cerebral edema, and length of survival from 2 hours to 12.5 hours. Coe reinforced these results with a follow-up percussion brain injury experiment. He showed that a single 3.0 ATA/60 HBOT with 2% carbogen immediately after injury resulted in a significant improvement in maze running ability over controls at seven days that was nearly equal to non-injured animals. Sukoff (1968), using cerebral implantation of psyllium seeds in dogs, delivered HBOT beginning 24 hours after surgery at 3.0 ATA/ 45 (total dive time?) three times/day tapering to once or twice/day, and found a reduction in cerebral edema and cisternal fluid pressures and an increase in survival. In another model of cryogenic injury Miller, Ledingham, and Jennett showed that a single HBOT at 2.0 ATA/15-30, beginning minutes after injury, reduced ICP, but at 40-60 minutes the reduction in ICP began to reverse and rebounded (in some dogs) above baseline on return to air breathing. With the same model Miller and Ledingham later showed that HBOT at 2.0 ATA/4 hours, beginning one hour after injury, caused an initial reduction in ICP that progressively reversed and then significantly rebounded post HBOT. Simultaneously, CSF lactate increased to the levels of controls, contrary to Holbach's experiment above. A third experiment by this group in the same model confirmed the benefit of short exposures of HBOT at 2.0 ATA. Dogs subjected to 2.0 ATA/15 had a 33% reduction in ICP and an improvement in perfusion pressure while dogs at 3.0 ATA/15 had a reversal of ICP reduction and rebound after return to surface, indicating a toxic effect of this pressure. Kanshepolsky subjected cats to cryogenic brain injury and treated with HBOT at 2.5 ATA/90 three times/day for upto three days, beginning either two or 6 hours after injury. HBOT increased survival and decreased brain edema if begun two hours after injury, but had no significant effect if treatment was delayed to six hours. A summary of the HBOT/cerebral edema studies in animals is that HBOT has two different effects (Hayakawa): one reducing brain edema (injured brain), and another producing brain edema (normal brain). This toxic effect on normal brain causes a breakdown in the protective vasoconstriction of arterioles, resulting in a rapid rise in brain blood flow and deterioration in EEG (Holbach). If not reversed seizures follow (Bean), (Chavko). It appears that high pressures (greater than or equal to 2.0 ATA) maybe beneficial for very short periods of time (15-30 minutes) if delivered within a few hours after acute brain trauma. A similar conclusion has been reached in global ischemia/anoxia/coma (Harch, Jain). These pressures, however, have a toxic effect if used for greater duration and beyond the 2-3 hour post injury period. During

this later period 1.5 ATA/30 minutes appears to be the optimal pressure/duration (human data).

HBOT also has beneficial effects on cellular reperfusion injury. Both Zamboni and Thom have reported inhibition of white blood cell mediated reperfusion injury at 2.0 and from 2.0 to 2.8 ATA, respectively, when HBOT is initiated within approximately one hour after brain insult. This is consistent with the data above on high pressure HBOT in cerebral edema immediately after brain injury. Unfortunately, this may not be applicable to human TBI and its associated reperfusion injury since time to initiation of HBOT is often many hours after injury.
The non-controlled human data is equally positive and consistent with the animal data. Mogami, in 66 acute coma cases, 50 of which were severe TBI, reported neurological improvement in 50% and EEG improvement in 33% of cases with a decrease in CSF pressure, occurring mostly at depth, that regressed or rebounded post treatment. The patients also exhibited a slight improvement in cerebral aerobic metabolism with a slight decrease in the lactate/pyruvate ratio. The best responses were in the least injured patients. Treatment pressures were 2 ATA/60 minutes, once or twice/day with an average of two treatments. The preponderance of benefit at depth with regression/rebound post treatment suggests an excessive pressure of oxygen as reviewed above in the cerebral edema animal studies. Hayakawa achieved similar results in 9 acute TBI and 4 post-op brain tumor patients at 2ATA/60 minutes, measuring CSFP. He found three patterns of response, the most common of which was a reduction of CSFP at the beginning and a rise at the end of HBOT. He proposed the edema reducing effect of HBOT on injured brain and edema producing effect on normal brain mentioned above. Both of these studies are reinforced by the two companion studies of Holbach on EEG and rCBF above in 14 acute severe TBI patients exposed to different pressure profiles.. This data is strongly supported by Holbach's additional report in 1977 on metabolic data in the same or a similar group of severe acute TBI (n=23) and CVA (n=7) patients, also noted above. This metabolic data is further supported by Holbach's 1974 report on crude outcomes of 102 patients, 43 with "life-threatening" acute TBI, who were treated with an average 2.6 HBOT's within a few days of injury: 52 at 2-3 ATA and 50 at 1.5 ATA. The TBI subset treated at 1.5 ATA demonstrated a 33% increase in the number of markedly improved patients. Additionally, Lareng published two cases of deepening coma secondary to TBI who were treated 4 and 10 days post TBI at 2.0 ATA/45 bid for 42 treatments. One patient was completely well with a normal EEG and the other had complete neurological recovery. Belokurov treated 23 acute pediatric coma cases, 13 of which were traumatic, at 1.7-2.0 ATA/60, once/day for four days. He found: a 50% reduction in time of coma if HBOT was initiated within the first 24 hours after injury (indicating HBOT responsive pathology in this period of time), a statistically significant improvement in coma score after the first HBOT, especially in the TBI patients, and further improvement in eight of ten patients who were retreated with HBOT after relapse into vegetative coma. In contrast, Artru measured CBF and metabolism in 6 severe acute TBI patients 5-47 days post injury with 2.2 or 2.5 ATA/90 minute HBOT exposures and found variable responses due to differential effects of HBOT on injured and normal brain.

Curiously, systemic arterial PO2 declined in 8 of 9 measurement trials, indicating a pulmonary or severe brainstem toxicity/complication with this profile.
All of the above human studies were performed on severe acute TBI patients a few days post injury. The data is remarkably consistently positive, but the exact dose of oxygen is less clear. In general, the data suggests that approximately 48 hours or more after injury pressures from 1.5 to 2.0 ATA and treatment times less than or equal to one hour have reproducible beneficial effects and that pressures above 2.0 ATA have negative effects on CBF, EEG, CSFP, and aerobic metabolism. Specifically, higher pressures seem to reverse the brain's protective vasoconstrictive capacity leading to a marked increase in CBF/CSFP and simultaneous deterioration in EEG/aerobic metabolism. Moreover, there may be competing effects in injured and normal brain that determine whether the final result is positive or negative based on the relative proportions and possibly locations of the two types of tissue. Unfortunately, due to small numbers of patients and inadequate data this complex relationship cannot be adequately defined for all of the different levels of injury at different times of intervention.
The more rigorously controlled human clinical studies recapitulate all of the above data/conclusions and lead to more powerful conclusions. Holbach followed his 1971 study with a randomized prospective controlled study of HBOT vs. standard intensive care in 99 acute TBI coma (mid-brain syndrome) patients, 2-10 days post injury. The HBOT patients received 1-7 treatments at 1.5 ATA/45 minutes. The HBOT group achieved a 21% decrease in mortality and the apallic state (vegetative coma) and a 450% increase in complete recovery. Artru published a similar RPCT on 60 acute coma TBI patients 4.5 days post injury. HBOT patients were delivered 2.5 ATA/90 minute treatments once/day on a 10 day schedule with a four day break and then repeat of the cycle until consciousness or death. Despite multiple breaks in protocol, delays to treatment, and use of the a high pressure, one of 9 subgroups, the brainstem contusion group, experienced a significantly higher rate of recovery of consciousness at one month. Lastly, and most importantly, Rockswold in 1992 reported the most exhaustive, rigorous, and important study to date in acute TBI in an attempt to refute or affirm all of the above animal and human data. Conducted from 1983 to 1989 the study enrolled 168 patients with GCS of 9 or less in a RPCT design and stratified the patients by age and GCS. Patients were treated at 1.5 ATA/60 every 8 hours for a maximum of two weeks immediately post TBI or until awake or deceased during these two weeks. The average patient entered treatment 26 hours post TBI and received 21 treatments. Overall mortality was significantly reduced 50% in the HBOT group and as high as 56% and 60% in the elevated ICP and GCS 4-6 subgroups, respectively, however there was no difference in the good outcome categories between the groups at 12 months.
A summarization of the above data demonstrates an undeniable beneficial effect of HBOT on mortality and recovery of consciousness and a suggestion of improved neurological outcome. The best results were achieved at pressures less than 2.0 ATA, specifically 1.5 ATA. Unfortunately, there is not a large amount of data generated from finely adjusted dose escalations of HBOT, but rather a preponderance of studies performed at 1.5 ATA based on early dose escalation studies, with some comparison data at 2.0 ATA and higher. These conclusions are derived from a number of RPCT's that en block constitutes one of the most powerful and consistent bodies of scientific evidence for any accepted indication for HBOT. The TBI controlled trials alone already

exceed the data for at least six of the thirteen indications, including the last addition, cerebral abscess. While internally consistent and stand alone sufficient this body of data was recently strengthened by the addition of the followup article of the Rockswold group in March, 2001.

On a group of severe TBI patients similar to those in the 1992 study the authors methodically and meticulously studied brain metabolism at 1.5 ATA, once/day for 5-7 days post injury. They found that HBOT improved the cerebral metabolic rate for oxygen and decreased CSF lactate , especially in those with reduced CBF or with ischemia, normalized the coupling of CBF and cerebral metabolism, exerted a persistent effect on CBF and metabolism, and reduced elevated levels of ICP and CBF. Notably, HBOT's recoupling of flow and metabolism is the only demonstration of such in the history of science. They recommended that shorter (30 minutes) more frequent (every 8 hours—identical to their first study) treatments would optimize treatment.

This final study reaffirms the multiple studies above at both lower and higher pressures that show reversal or deterioration of a beneficial HBOT effect after 30+ minutes in the chamber. The data and scientific argument is strong and supports/demands low pressure HBOT in acute severe traumatic brain injury. Some of the studies suggest that even a few treatments can have a profound effect. The protocol is uncertain beyond the first two weeks, but should probably be delivered according to the principle employed in medicine for any therapeutic modality: treat until clinical plateau. While the data is not so consistent on long-term neurological outcome, this goal should be left to further research and multi-modality therapy. After all, the first priority in life-threatening illness is to save the patient.

As a matter of perspective, the American Heart Association has spent hundreds of millions if not billions of dollars on CPR education, training, and research, yet has still have made very little progress in successful resuscitation of cardiac arrest. Very few survive and almost all who survive are severely neurologically impaired. Despite these dismal results the research largesse continues in an effort to find even the smallest improvement in mortality. At our fingertips is possibly the therapeutic modality with the greatest and most dramatic effect on reduction of acute TBI mortality in the history of medicine. The neurosurgeon authors of the Rockswold study conclude that "HBOT should be initiated as soon as possible after acute severe traumatic brain injury." I believe the UHMS and medical profession should follow their lead and the UHMS list acute TBI as an accepted indication for HBOT. I am ready, willing, and eager to defend this position. Thank you for the opportunity.

Sincerely,

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