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TRAUMATIC BRAIN INJURY

Pathophysiology

Etiologies resulting in a traumatic brain injury (TBI) can be head impact, blast or combination of both. A more rare etiology is an internal only impact from the head being vigorously jostled as seen in shaken baby syndrome. Impact related injuries occur from the brain hitting the intracranial surfaces in a back and forth manner (coup/countercoup) resulting from acceleration and deceleration forces.

From a physiological aspect, head trauma causes microvascular injury and a neurometabolic cascade starting with augmented sodium-potassium pump efforts to restore the neuronal membrane potential. The increased demand for andesine triphosphate via the Krebs's cycle depletes available glucose due to diminished cerebral blood flow. The cascade continues as depressed metabolism allows increased calcium impairment for mitochondrial oxidative metabolism leading to neurofilament and microtubule disruption, axonal injury, impaired neuroconductivity, neuroinflammatory response and cell death (1). These postconcussive cascade effects create a vulnerability for repeat injury and comorbidities manifested by clinical symptoms and potential for chronic or degenerative neurologic changes (2). Ma (3) describes the axonal dysfunction and degeneration by calpain activity as the underlying event to common neurologic diseases. This protease has also been implicated in a similar demyelination of neurons seen in the progress of pathology associated with chronic TBI (4).

Hyperbaric oxygen therapy (HOT) counteracts many of the adverse aspects of traumatic brain injury from initial insult to chronic exteriorization. The obvious effect is return of mitochondrial metabolism subsequent to cerebral perfusion pressure and brain tissue oxygen (5). HOT also aids in angiogenesis, brain microstructure integrity, and increase in white matter tracts (6). Finally, hyperbaric oxygen abates the effects of reperfusion injury resulting in decreased neuroinflammation (7). For an in-depth review of traumatic brain injury pathophysiology and HOT actions refer to Hadanny (8).

Symptoms

Symptoms manifested in mild TBI (mTBI) or concussion can be categorized as Emotionality (sadness, nervousness, irritability and generally more emotional), Somatic (headaches, visual problems, noise/light sensitivity, dizziness, and nausea), Cognitive (attention problems, memory dysfunction, cognitive slowing, fogginess, and fatigue) and Sleep Disturbance (difficulty falling asleep, and sleeping less than usual (9). Severe TBI (sTBI) includes higher levels of trauma including penetrating injuries, brain contusions/avulsions, and hemorrhage with Glasgow Coma Scores (GCS) of 3-8 (Coma: unconscious state, no meaningful response, no voluntary activities) (10)

ACUTE TRAUMATIC BRAIN INJURIES

Acute mild traumatic brain injury has recently focused on athletic etiology although simple falls or motor vehicle accidents, etc. are common. The National Collegiate Athletic Association (NCAA) and the US Department of Defense (DoD) established the Concussion Assessment, Research and Education (CARE) initiative in 2014 (11). CARE created a national multi-site consortium to conduct a prospective, longitudinal, multi-sport investigation to delineate the natural history of male and female concussion by incorporating a multi-dimensional assessment of standardized clinical measures of post-concussive symptomatology and performance based testing (cognitive function, postural stability and psychological health). Advance research includes blood biomarkers, MRI, genotyping, and sensor technology.

Evaluation: Collegent members' concussions result in a well defined monitoring and evaluation including the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Standardized Assessment of Concussion (SAC), Balance Error Scoring System (BESS), Sport Concussion Assessment Tool-3 (SCAT3), Brief Symptom Inventory-18 (BSI-18), Neurobehavioral Symptom Inventory (NSI) and neurological examination. One advantage is that most university members and the NFL do preseason test arrays to establish baselines. This creates a snapshot to establish a goal for therapy. Many high schools have started similar tests and preseason baselines. For a non-athletic concussion, choosing a questionaire (NSI or SAC.) or a computerized assesment (ImPACT or SCAT3) to give a patient will allow a means to monitor therapy improvement. They also have population references to give a reasonable idea of a baseline for the individual.

Treatment: Concussion standard of care treatment consists of cognitive and physical rest for 48 hours, then gradual supervised activity until the individual is asymptomatic and monitoring tests are acceptable before eligibility to return to duty or play is determined, about 7 days. If symptoms persist, the individual should not be returned to play or duty. Typical guidelines produced by the University of Wisconsin and the state Public Health Service follow the above concepts (12).

Hyperbaric oxygen has been proposed from an acute mTBI perspective from the philosophy that it will be more effective the closer HOT is used to the initial injury. This principle drives other accepted neurological indications such as central retinal artery occlusion and sudden idiopathic hearing loss. A proposed study protocol at one of the Care and consortium academies would see if five daily hyperbaric oxygen treatments at 2.0 ATA for sixty minutes would decrease the time to baseline versus standard of care. The referenced tests above would be given after day three and day six treatments. The author has heard of anecdotal reports of 2.0 ATA for the first two days followed by 1.5 ATA treatments for the following three days, but no reference could be found with online searches. At this time either protocol would be acceptable. As this is a relatively new population, eventual results of studies and case seeries should eventually be published. As the academy was part of the CARE longitudinal study, there would be potential to see if hyperbaric oxygen used for the study concussions would prevent the late effects of concussion when compared to the standard of care subjets.

ACUTE SEVERE TBI

Pathophysiology and Hyperbaric Effects

Physical impact to the head can result in brain contusions especially under the initial impact site, hemorrhage, white matter tract shearing resulting in diffuse axonal injury, and cerebral edema. Penetrating skull injury by impalement, blunt force or shrapnel and bullets cause direct brain injury.

Animal studies in the 1960's demonstrated benefits of hyperbaric oxygen in pressures from 2.0 to 3.0 ATA such as cerebral vasoconstriction, decreased cisternal cerebral spinal fluid, decreased cerebral edema and decreased mortality compared to the control animals. Human studies began in earnest in the 1970's. Artru (13) showed when there is cerebral edema or intracranial hypertension, HBO can improve cerebral blood flow (2.5 ATA for 1 hour). Halbach (14) in a study of TBI and anoxic brain injury patients used pressures of 1.5 ATA and 2.0 ATA. He found glucose metabolism improved and arterial-venous differences of oxygen remained constant with 1.5 ATA (up to 40 minutes) from baseline measurements. Contrarily, the 2.0 ATA patients did not tolerate more than 15 minutes of treatment. Rockswold identified favorable outcomes (50% reduction in mortality scores) in sTBI related to those subjects with GCS scores of 4-6, mass lesion, and increased intracranial pressure (15). The follow-up study demonstrated an increase in tissue oxygenation that lasted at least 6 hours after the hyperbaric treatment. This resulted in improved cerebral metabolic rate of oxygen, a significant decrease in intracranial pressure, and a decreased cerebral spinal fluid lactate levels that also lasted over 6 hours (16). In 2013, Rockswold used a combination of 1.5 ATA oxygen for one hour followed by three hours of normobaric hyperoxia (100% oxygen - NBH) versus standard care. The combination appeared to work synergistically and treatments improved oxidative metabolism markers and injured brain as well as pericontusional tissue. It also reduced intracranial hypertension and improved cerebral toxicity markers without brain or lung oxygen toxicity. In addition there was an improved Glasgow Outcome Scale (GOS) favorable outcome as well as a reduction in mortality (17). In a study review, Crawford compared hyperbaric oxygen therapy vs. standard care resulted in a weak recommendation in favor of HOT when patients had positive alterations in the level of consciousness, favorable GOS (example:1 to 3 or good recovery, moderately disabled, and severely disabled) and decease in mortality were considered factors (18). Daly (19) did a systemic article review of HOT in the treatment of acute sTBI. The review demonstrated improved physiologic measures that did not cause pulmonary or cerebral toxicity. They also showed improve clinical outcome.

In light of the review studies it appears that sTBI patients respond best to 1.5 ATA oxygen followed by 3 hours of 100% oxygen at normobaric pressures once a day for three days. However, the National Institute of Neurological Disorders and Stroke (NINDS) and the Strategies to Innovate EmeRgENcy Care Clinical Trials Network are doing a 200 subject, 10 arm study. The arms are as follows:

Arm	Pressure (ATA)	Frequency	NBH
1	0	0	Without
2	2	QD	Without
3	2.5	QD	Without
4	1.5	QD	With

5	2	QD	With
6	2.5	QD	With
7	1.5	BID	Without
8	2	BID	Without
9	2.5	BID	Without
10	1.5	BID	With

This study is described in ClinicalTrials (20) and by Gajewski (21). If completed, it will delineate optimal treatment protocols.

ACUTE TRAUMATIC BRAIN INJURY WITH ASSOCIATED BLAST INJURY

Pathophysiology

Blast injury has been mainly associated with military conflicts. Unfortunately, terrorist attacks as well as industrial accidents are becoming more commonplace. The pressure wave created by the blast will travel through the body at different speeds depending on the tissue density. Particularly in the blood and vasculature, the blast wave will create a rapid compression and decompression that can result in air emboli injury in tissue or within the vasculature. These emboli can travel anywhere within the vasculature and is particularly concerning the brain, heart, and intestinal tract and also been found to lodge in kidneys (22-24). One must recognize that primary blast injuries are caused by barotrauma from the pressure wave. Secondary blast injuries result from projectiles and shrapnel from the blast source. Tertiary blast injuries are caused by the blast wind that may throw victims against fixed objects resulting in blunt trauma. Quaternary blast injuries result from fire and building collapse resulting in burns and crush injury (25).

As HOT can be effective for cerebral air emboli up to 12 hours after the acute event (26), this allows the patient trauma, including pneumothorax, to be stabilized before treatment and should be considered. There is also some evidence that munitions and artillery can also result in mini-pressure waves that are repeated sufficiently to produce small emboli.

Technical Treatment Protocol

Pressure wave only with no evidence of other trauma but continued loss of consciousness is suspect for an air embolism etiology. The use of ultrasound to the chest can evaluate the existence of a pneumothorax. Treat if present using a device that can go into the hyperbaric chamber. A Heimlich valve type device can be secured similar to ambulance transfer and will allow gas to escape if the source of the pneumothorax is still leaking gas upon ascent, thus preventing a tension pneumothorax. Air embolism is typically treated with a U.S. Navy (USN) in treatment table six. However, there is a possibility of coup-contracoup injury to the brain with mTBI. Consequently a Hart-Kindwall table can be considered that will use a short duration, high pressure protocol to decrease bubble size and dissolve nitrogen to where the bubble dissipates. The protocol then decreases the pressure to levels used in acute TBIs.

The Hart-Kindwall protocol is as follows:

Descent rate—1-3 psi per minute to 26 psig pressure (2.8 ATA); initiate breathing 100% oxygen for 30 min; decompress to 14.7 psig (2.0 ATA) over 30 min; maintain 14.7 psig (2.0 ATA) for 60 min; decompress to surface over 30 min (about 0.5 psi/minute). The total elapsed time, not counting descent is 150 min.

As the patient is unconscious, tympanic membrane that rupture is possible. Pressure equalization tubes or myringotomy can be considered prior to the treatment. Evaluation of the patient after the treatment should be done. If any continued concussion symptoms are present, the patient can be treated daily for 60 minutes at 2.0 ATA as with the acute concussion protocol above.

Blast injury with secondary or greater category: stabilize injuries and use ultrasound to rule out pneumothorax. Treat pneumothorax as above, if present. Although a higher level of TBI may be present, potential air embolism in the brain, heart, or solid organs take precedence and the Hart-Kindwall protocol is recommended. If a sTBI or a mTBI is suspected, then the patient should be treated using the protocols above. One should also note that other injuries may benefit from the treatments and potentially result in fewer and less complicated surgeries as seen in compartment syndrome.

CHRONIC TRAUMATIC BRAIN INJURY/POST-CONCUSSION SYNDROME

By definition, chronic TBI is one with continued symptoms 90 days after the concussive event. Common symptoms are headache, dizziness and disequilibrium, visual symptoms, fatigue, sleep disturbance, cognitive symptoms (including memory, attention, concentration, and executive function disorders), persistent pain, hearing difficulties, olfactory deficits, nausea, changes in appetite, numbness, vertigo, and neuropsychiatric symptoms including behavioral and mood changes, confusion. Department of Veterans Affairs (DoVA) guidelines (27) concentrate on isolating and treating each symptom with both pharmacological and non-pharmacological methods.

Pathophysiology and Hyperbaric Effects

Previous pathophysiology for the acute phase above remains relevant. As with concussion, CO poisoning causes neurometabolic cascade events. Post CO poisoning, the protease calpain has been linked as a cause of demyelization seen in delayed neuropsychiatric syndrome. HOT has been demonstrated to prevent CO poisoning delayed neuropsychiatric syndrome. Calpain has been linked to similar demyelination in TBI seen in post-concussion syndrome (PCS). Wolf describes this relationship in detail. (9).

Interest in post-concussion syndrome treated with hyperbaric oxygen started in earnest as a result of military casualties from the 1991 and 2002 Middle East conflicts. The use of HOT to treat PCS started with anecdotal online reports around 2006 and precipitated research studies by civilian institutions and DoD and Israeli military. The first DoD study used 100% at 2.4 ATA (45 feet sea water) for 90 minutes exposure compared to a 1.3 ATA air exposure for 90 minutes. The first publication demonstrated that hyperbaric oxygen in the TBI population was safe. There were no significant differences between the two groups with the predominate side effect of ear and sinus blocks. There were no seizures and there was actually an improvement in visual acuity in many of the subjects (28). A second public publication from the same study showed that there

were certain subgroups that improved in the treatment group compared to the control group that related to the time from the blast concussion, loss of consciousness, etiology of the concussion, as well as correlations with several cognitive subtests (9). A third publication from the study showed a correlation in the activation of stem cells with cognitive improvement (29). Stem cell activation increases with increased pressure.

The USN/DoVA study used a 2.0 ATA pressure with three randomized groups. One group rate of 100% oxygen, the second using a 75% Nitrox that simulated 100% oxygen at 1.5 ATA and a third using a 10.5% Nitrox to simulate breathing air at 1.0 ATA. Each exposure lasted one hour. The results demonstrated no significant differences between the three groups on any of the individual symptom inventory items or subscale scores in the Rivermead questionnaire immediately after the series, at one week after the series, or three months after the series. The study also showed no beneficial effects of hyperbaric oxygen exposure for symptoms, functional tests or cognitive or psychomotor performance at either 1.5 or 2.0 atmospheres equivalent (30-32).

The U.S. army study (33) randomized groups into 1.5 ATA 100% oxygen, 1.2 ATA air and standard of care. The hyperbaric exposures for 60 minutes. The study concluded that there were no significant changes between the compression exposure groups. Weaver relates from the DoD/DoVA guidelines that "there is no treatment standard of care for this condition or standardized follow-up assessments of treatment using validated instruments" (34).

All three of the DOD studies reported no significant differences between the treatment and the control groups. However, both groups improved. This originally was felt to be due to placebo effect. Letters to the editor pointed out that the control groups may have been an alternative treatment group due to hydrostatic pressure effects as well as increased partial pressure of oxygen. This was discussed by Wolf (9) and indeed the control groups could have been alternative treatment groups. Boussi took the hydrostatic pressure issue away by treating TBI subjects with hyperbaric oxygen by using a crossover design (35). Essentially two groups were treated at 1.5 ATA for one hour for 40 treatments. However, one group was initially treated whereas the second group underwent routine care for two months before the above HOT was given. The study demonstrated improvement in cognitive function quality of life, and cerebral blood flow only when HOT was given.

The first DoD study based its design from the Agency for Healthcare Research and Quality's future research recommendations (36) from its 2002 review of hyperbaric oxygen for TBI, stroke and cerebral palsy. Below are the pertinent comments.

1. "The dosage and duration of treatment must be determined in carefully designed dose-ranging studies before definitive studies demonstrating clinical efficacy can be started'. For the most part, this has been done with 100% oxygen doses from 1.5 to 2.4 ATA as well as pressurized air alternative doses.

2. "Uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT. The case against HBOT is based on the reasoning that, *because HBOT may be harmful, it must be held to the highest standard of proof.* A corollary is that, if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its

efficacy can be lowered". Results of the studies up to 2.4 ATA has demonstrated safety for all of the treatment protocols. The main concern upon initating chronic TBI studies was if the condition itself would predispose subjects to oxygen toxicity seizure as occasionally seen in acute sTBI (and DCS or CO poisoning). None of the studies have reported a seizure, likely due to stabilization of the brain. Even in patients with DCS or CO poisoning who have a seizure during treatment, the treatment is paused until 15 minutes after the post ictal phase, then HOT is resumed per the protocol. Hadanny's recent retrospective study (37) demonstrated one oxygen toxicity-induced seizure with an overall incidence of 1:62,614.

3. "*Patients' unwillingness to be assigned to a placebo or sham treatment group* is another barrier to conducting controlled trials". Studies have not had true placebo treatment groups with the exception of HOPPS and the crossover study. HOPPS had standard of care which essentially remained the same (or worsened) in the outcome measures whereas both exposure groups improved. AHRQ also comments, "Whether placebo-controlled trials are necessary to evaluate HBOT has received a great deal of attention in discussions about HBOT. Participants on all sides of this debate make the assumption that an "evidence-based" approach implies devotion to double-blind, placebo controlled trials without regard to practical or ethical considerations. This assumption is false. Double-blind, placebo-controlled trials are the "gold standard" for government regulators overseeing the approval of new pharmaceuticals, but not for clinical decision-making or insurance coverage decisions. Evidence-based clinical decisions rely more heavily on comparisons of one treatment to other potentially effective therapies, not to placebos."

4. "*Relevant outcome measures.* Some of the most important outcomes of treatment are difficult to measure". All studies have attempted to use outcome measures that seem reasonable, but have inherent values as well as detriments. In clinical decisions, whether lab values or measuring wound size, we look for the differences of our outcomes over time to determine success of failure. The use of HOT for TBI needs to have at least one objective measure for each relative component derived from the TBI.

AHRQ also commented "If there is a 1 percent chance that the treatment works, a rational decision maker would try it – there is a potential gain and no potential loss. On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it". The VA/DoD Clinical Practice Guidelines define a "B evidence rating" as "a recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm".

Chronic TBI treatment using hyperbaric oxygen is in a similar position as acute severe TBI as far as treatment protocols. Due to the above studies and observational reports, many states have passed legislation to treat Veteran Service Members with hyperbaric oxygen for TBI and post-traumatic stress disorder (PTSD). Ideally, data regarding pressure, duration, number of treatments in a series, booster treatments, and specific measurable outcome measures should be collected in a registry similar to what was done with HOT for radiation injury. As the crossover design study has demonstrated potential improvement of HOT, current recommendations would

be pressures of 1.5-2.4 ATA for 60 to 90 minutes. A range of pressures and duration is congruent with most of the other indications for hyperbaric oxygen therapy.

Disclaimer

The opinions expressed in this document are solely those of the authors and do not represent an endorsement by or the views of the United States Air Force, the Department of Defense, or the United States Government.

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