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Crystal Amundson

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New Treatment Options for Concussions Using Hyperbaric Oxygen Therapy

By: Crystal Amundson

Eric Van Hecke, PA-C

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Abstract

Background: Millions of Americans experience concussions every year. With new attention from the media looking into the long-term sequela of concussions, more research and studies are initiated to find an effective treatment. Concussions happen after an impact to the head or body that causes a pathologic disruption in normal brain function. Symptoms most commonly associated with the trauma are headaches, emotional distress, vestibular disturbances and sensitivity to light. Historically, treatment has been physical and cognitive rest.

Methods: A systematic search of PubMed was performed to identify articles pertaining to the use of hyperbaric oxygen therapy in concussions and traumatic brain injuries in all settings including; adults and children, sports related, civilian and service members. Clinical trials, review articles and animal studies were included, and research was synthesized to review the effect of hyperbaric oxygen therapy on concussions.

Hyperbaric Oxygen Therapy: Treatment employs increased atmospheric pressures and 100% oxygen to diffuse pure oxygen into hemoglobin and plasma, increasing oxygen saturation in hypoxic environments by as much as 700%. Hyperbaric oxygen therapy is not a new treatment but has not been approved for many neurological diseases. Use of this therapy has been found to be quite safe and research has proven it to be effective.

Conclusion: More studies on the use of hyperbaric oxygen for concussion therapy is needed to support evidence-based medical decision making. Optimistic civilian and military patients worldwide hope that research will continue, and hyperbaric oxygen therapy will become a mainstay treatment for all scopes of severity in traumatic brain injuries.

Introduction

Concussions are becoming a serious health concern throughout the world. The CDC states that approximately 1.6 to 3.8 million concussions occur in sports and recreational activities every year.[1] Approximately 3.1 billion people were living with traumatic brain injuries (TBI) with the health-care cost estimated to be $76.5 billion in 2012.[2] Researchers believe this number is underestimated, as a considerable number of the population does not seek medical attention after a head injury.[3,4] From 2006 to 2014 the number of concussions reported rose 53%.[5] Public awareness through media and increased research have shown the consequences of multiple concussions, and inferably explain the increasing concussion incidence rates.[6] With the rise in reported concussions, treatment protocols are rapidly evolving and processes to identify the best treatment for each patient continue to be investigated.

Concussion is defined as biotechnical force to the face, head, neck, or body that results in a rapid onset of impaired neurological function as defined by the most recent Conesus Conference in Berlin, Germany.[7] A fall, motor vehicle accident, sports injury or abuse are all major causes of concussions and traumatic brain injuries (TBI) every day.[1] Falls are the most common cause, particularly in children and older patients.[8] Symptoms may last for days to weeks, with symptom decline being the best indicator for recovery.[1] Every person's symptoms vary, which makes treating them with standard protocols difficult. Concussion symptoms can affect all aspects of a person's life; at school, at home, at work, and during sports or recreational activities.[6] With this many facets of life affected it is particularly important to tailor each patient's treatment plan and "return to life" timeline.

The clinical manifestations and physiologic sequela associated with concussion are largely recoverable with time, but repeated concussions, especially within a window of

vulnerability, may lead to more chronic post concussive syndrome (PCS) or even neurodegeneration for patients.[9] Multiple concussions are now known to increase long-term mortality, reduce life expectancy and are associated with increased occurrences of seizures, sleep disorders, neurodegenerative diseases, neuroendocrine dysregulation, and psychiatric diseases.[10] Depression is the most treated side effect of concussions.[8] Many other non-neurological disorders have been known to arise and persist for months to years' post-injury, such as sexual dysfunction, bladder and bowel incontinence, and systemic metabolic dysregulation.[10]

The goal of this paper is to review the literature associated with a new treatment protocol using a method that was first developed in 1662 to treat decompression sickness. Hyperbaric Oxygen Therapy (HBOT) is now being used in treatment of concussions in all domains; including military, civilian and sports related concussions.[7] This thesis, will examine the results of HBOT literature review in the treatment of concussions.

Research has shown that untreated brain insult is one of the most expensive health issues for society. Intensive occupational therapy and rehabilitation programs are considered essential for maximizing quality of life after injury but are often only moderately successful. Clearly, new methods for brain repair should be assessed in order to provide continued relief to suffering and disabled patients.[11] Therefore, determining the most successful treatment protocols would benefit patients and the health care system worldwide.[12]

Abbreviated terms:

HBOT: Hyperbaric Oxygen Therapy, NBOT: Normobaric Oxygen Therapy, TBI; Traumatic Brain Injury, PCS: Post-Concussion Syndrome, PPCS: Persistent Post Concussion Syndrome, DTI: Diffuse Tensor Imaging, MRI: Magnetic Resonance Imaging

Methods

PubMed was used to search and identify relevant articles to this thesis paper. Searches included “Concussions”, “TBI”, “hyperbaric oxygen therapy” and “neurogenesis”. Results were narrowed to research within the last 20 years. Inclusion criteria for this systematic review involved evaluating study designs and assessing the authors’ interpretation of their data sets. Randomized control trials, retrospective observational non-interventional studies, prospective observational studies, prospective interventional trials, meta-analyses, and animal trials were all included. Each article was reviewed independently, and information was then collected for this review.

Background

At the most recent Concussion in Sport Conference in Berlin, the group recommended that concussion and mTBI be separate terms, reasoning that concussion typically ends in complete recovery, while mTBI is associated with more persistent symptoms.[4] The World Health Organization defines TBI as having one or more of the following characteristics: is permanent, caused by non-reversible pathological alterations, requires special training of the patient for rehabilitation, and/or may require a long period of observation, supervision, or care.[10] Predicting a patient’s recovery progression is quite variable and there are many factors related to concussion recovery time that are not yet well understood.[1] Those with delayed recovery, or persistent post-concussion syndrome (PPCS), may have risk for other factors that are just now being studied; including post-traumatic amnesia, more severe acute symptoms, younger age, prior history of concussion, female gender, prior psychiatric condition, and prior migraine history.[1,4] Iverson reported on several of these studies including a connection between prior concussions with inferior clinical outcomes after concussions and others with an association

between prior mental health history all showing an association with worse outcomes.[13] Additionally, there has not been shown a clear association between ADHD, other learning disabilities or migraines and less successful outcomes.[13]

Up to 25% of all patients experience PPCS in which the symptoms last for over 6 months.[8] Sport-related concussions have received increasing press attention over the past decade, driven in part by high profile cases involving former professional athletes who have suffered from debilitating and life threatening mental health conditions, and the heightened incidence of chronic traumatic encephalopathy (CTE), a progressive neurodegenerative disease found in individuals with a history of repetitive brain trauma.[14] As a result, a number of public health initiatives such as the Centers for Disease Control and Prevention's HEADS UP program, National Football League's Play Smart, Play Safe, and many other research programs have pushed advancements in concussion prevention, injury detection, and post-injury treatment and management strategies.[14]

Epidemiology

The epidemiology of concussions, like its reported numbers, may vary extensively due to the mild nature of some such as a rash, to no outward signs to alert the patient. Another element of concussion is the fear of being taken out of sports or restricted from some military work, that may skew true epidemiology reports of concussions.[6,8] Research states males sustain more concussions than females, in sports with equivalent rules played by both genders, like soccer, basketball, softball/ baseball, while females have about twice the rate of concussion as males.[9] The reasons for these gender differences are unclear; most research has focused on differences in neck strength, hormonal differences or variances in symptom reporting.[9]

Pathophysiology

Understanding the pathophysiology of concussion can help guide management and treatment focusing on the underlying mechanism and translating them to recovery.[4] Directly preceding a force that concusses the brain, a neurometabolic cascade begins. This force causes cellular membranes to rupture and ions to shift in and out of cells.[15] As the brain tries to restore homeostasis, energy requiring ionic pumps begin to work in overdrive, causing high glucose expenditure and eventually depletion of energy stores.[15] This hyperglycolosis state can last from 7 to 10 days and is associated with cognitive impairments that we see as symptoms. Figure 1 shows a timeline of ion and metabolic shifts.[15] When the brain is going through these ion and metabolic shifts, it is most vulnerable to second impact syndrome and irreversible damage.

Axons are also very vulnerable to injury. Diffuse axonal injury (DAI) is a common neuropathological finding after concussion causing diffuse white matter lesions and is a major contributor to morbidity after TBI.[4] The main force is impact-acceleration, which deforms the brain, causing shear stress and stretch on the microtubule and neurofilament fibers that cause decreased neuronal transmission.[15] Multiple brain regions may be affected resulting in a variety of neurologic impairments; most commonly, these include the corpus callosum, brainstem, and thalamus.[4]

The central nervous system relies exclusively on aerobic metabolism and needs a high supply of oxygen to function appropriately.[16] When this aerobic metabolism is disrupted, complications are seen in neuronal signal transduction, like synaptic transmission, action potential and nerve excitability.[16] Cerebral blood flow is normally constant, regulated by receptors that monitor rapidly shifting arterial CO_2.[4] However, after an impact, vasoreactivity is impaired and has been linked to post-concussion symptoms that occur during limited exercise.[4]

The mechanism is believed to be a decreased endothelial and smooth muscle responsiveness due to enhanced endothelial nitric oxide production after trauma.[4]

The increased metabolic demand and the decreased cerebral blood flow lead to an energy crisis within neuronal tissue. These are believed to be the primary cause of the most common symptoms of concussion.[17] The link between acute pathophysiology and chronic changes after concussion is an area of high priority for researchers, but no direct causations have yet been proven.[9]

Many hypotheses are being tested. Current evidence suggests that for the most part, a single concussion is recoverable and that the likelihood of chronic dysfunction is lower in isolated cases and much higher in repeated concussion or concussions before recovery.[9] Understanding the potential mechanisms and physiology related to various symptoms and injuries that occur with a concussion are important in furthering our knowledge about concussion.[1] Greater knowledge about these changes may aid in concussion diagnosis as well as concussion management.[1]

Clinical Manifestations

The history of present illness, important to patient care in general, is also crucial to the diagnosis of concussions. Following a concussion, patients may experience both short-term and long-term effects that have ranging signs and symptoms. The short-term effects may include confusion, memory disturbance, the loss of consciousness, slowing of reaction time, loss of coordination, headaches, dizziness, vomiting, changes in sleep patterns and mood changes.[1] Table 1 from Cleveland Clinic gives a full list of signs and symptoms that may occur during a concussion.[17]

Symptoms typically resolve in a matter of days, however, many experience lingering effects that can last for weeks or months following the injury. This is referred to as post-concussion syndrome.[1] Severity of symptoms also ranges from mild to severe, with the latter relating to a more severe (acute) injury. Symptoms of concussion should gradually improve. While they may be exacerbated by certain activities or stimuli, the general trend should be of symptom improvement.[19] If symptoms are worsening over time, alternative explanations for the patient's symptoms need to be explored further.[17]

Clinical recovery is defined functionally as a return to normal activities, including school, sports, or work following an injury.[13] Operationally, it incorporates a resolution of post-concussive symptoms and a return to normal balance and cognitive functioning that is very near to preinjury proportions.[13]

Testing

Concussion diagnosis is primarily based on clinical judgement of the provider, with the use of close family members to recognize differences in the patient, and a variety of subjective testing.[3] Accurate diagnosis of concussion and evidence related to persistent symptoms remains subtle, in part due to individual and impact differences.[14] A thorough neurologic examination should be conducted for all patients with suspected concussion. This includes a mental status exam, full cranial nerve exam and balance exams.[17] These are typically the customary initial tests; any pertinent findings may prompt for further workup.[19] However, depending on the setting, patients may only be initially followed by an athletic trainer who may not have the skills to do a full physical exam.[3] Trainers do have their own set of exams that have been shown to be generally effective in indicating a positive concussion or the need for further examination or work up.

A number of assessments and the known relationships between these tests can support medical staff in making diagnoses and return to daily function decisions.[1] This should include baseline testing as well as timely evaluation post injury.[1] Owing to the variability of symptoms and the indeterminate time course for recovery, a multifaceted approach to concussion evaluation is warranted. This means, as a provider, working closely with the patient's athletic trainer or even their chiropractors may be frequently warranted.

The main exam used for concussions is pre- and post-concussion testing with a computerized neurocognitive assessment, which can evaluate memory, processing speed, problem solving skills, cognitive efficiency, and impulse control.[1] This assessment uses word discrimination, design memory, X's and O's, symbol matching, color match, and three letters that requires completion on a computer.[1] There are many different systems in use, with collegiate and high schools using ImPACT testing and researchers using NeuroTrax. Other necessary assessments include balance and gait measures that can be used to assess functional capabilities.[1] Many times, balance issues may affect patients for a long time after cognitive symptoms have abated. A somatosensory discrimination task is also used to measure peripheral and central sensory processing capabilities.[1]

One limitation to traditional neuropsychological assessments is their lack of sensitivity to detect underlying cognitive functions that may be impaired by 'silent' or not easily observable, concussive injuries.[14] Assessments that are not performed correctly, have even further constraints. It is imperative to learn and execute these assessments as clinicians. For this reason, researchers are using new advanced imaging modalities to closely observe changes within the brain.

Evaluations are normally done while the injury victim is with an experienced athletic trainer. The evaluation procedure is not always available in clinic or Emergency departments. While there are many recommended evaluations, there is no one gold standard assessment to date.[3] Many doctors, other medical professionals as well as engineers and inventors are searching for gold standard protocol for evaluating all patients with concussions. Hopefully, in the near future studies will reveal better ways to accurately diagnosis concussions. No substitute exists for clinical experience, training, and solid information on patient baseline personality and behavior change due to trauma.[3]

Imaging

Imaging is not a widely used modality for screening patients with possible concussions. As mentioned, if a patient has red flag symptoms, then imaging may be ordered but should be required. There are two widely used clinical decision tools employed in the emergency department for use in head CT following head injuries; the Canadian Head CT Rule and the New Orleans Criteria.[18] Other imaging modalities, which are not usually used in the diagnosis of concussions include Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). However, research states that the sensitivity of classic anatomical imaging techniques are not adequate in detecting pathophysiologic effects of concussion.[19] Due to the low sensitivity of standard clinical imaging, exploration has been shifted to advanced imaging techniques that may detect functional injuries.[3]

New techniques are increasingly employed for the objective evaluation of concussions, especially in research settings, including Diffuse Tensor Imaging (DTI), functional MRI (fMRI) and dynamic susceptibility contrast MR.[4] DTI is used to reveal the combination of axonal injury and secondary gliosis with local microvascular injury.[4] It is mainly used to expose the structural

integrity of white matter.[4] Diffusion tensor imaging measures the direction and restriction of the diffusion of water molecules, which is indicative of several white matter microstructural features, such as myelination, axon diameter, fiber density, and organization.[3] Fractional anisotropy (FA) and mean diffusivity (MD) are the two parameters that are typically reported in DTI findings.[3] Research has shown that an increased FA and a decreased MD are suggestive of positive findings in a concussion.[4]

Part of the functional MRI imaging involves susceptibility weighted imaging (SWI) and gradient echo (GRE) imaging allowing the visualization of microbleeds and to assess the damage incurred after injury.[4] Resting-state functional MRI can evaluate brain networks based on baseline energy expenditure, in awake and resting-state networks.[4] This might be useful to better understand the metabolic crisis occurring directly after an injury.

Dynamic susceptibility contrast MR perfusion can establish reduced cerebral blood flow (CBF), throughout and regional, as well as cerebral blood volume (CBV), which has been found to be reduced post-concussion.[4] This type of MRI uses blood-oxygen-level-dependent (BOLD) contrast, which distinguishes increased cerebral blood flow in areas experiencing increased neuronal activity.[3]

Recent reviews have emphasized major limitations of all advanced neuroimaging studies including small sample sizes, absences of baseline measures, and multiple statistical comparisons without adequate control for experimental error rate.[3]. The hopes are that these new scanning processes will better detect changes in microstructure and cerebral blood flow and oxygenation. With better techniques in viewing the changes within the brain after trauma, HBOT studies will have better results and reproducibility.

Outline of Current Treatments

What physicians and researchers know about concussions is increasing every year, but treatment for concussions has not been expanding at the same rate. Current treatment protocols look to physical and cognitive rest. Exactly what "rest" means and how long it should last are unknown, leading to a wide discrepancy in its presentation.[17] Cleveland Clinic recommended a period of rest lasting 3 to 5 days after injury, followed by a gradual renewal of both physical and cognitive activities as tolerated, remaining below the level at which symptoms are exacerbated.[17]

Physical rest and return to full activity is easier to follow and understand, while cognitive rest is much harder in this modern world full of television and smart phones.[17] Cognitive rest often includes avoiding reading, texting, playing video games, and using computers but is not limited to only these things.[17] Patient compliance in this area is usually low, especially in children who would rather be at school with their friends, than lying in bed resting.

Guideline procedures outline that patients should return gradually to work or school rather than try to immediately return to their pre injury level, much like with physical activity.[17] Gradual return in these areas allow for adjustments to be made and caught when the brain is being overly worked. Teachers need to be especially aware of a child's injury, as they are the ones that can assess the student's attention span or fatigue level, which are excellent indicators of an exploited brain.[17]

Other treatments include symptomatic treatment of headaches, sleep disturbances and emotional disturbances. Headaches are the most common post-concussion symptom that patients relate.[17] Usually, patients are able to tolerate NSAID use for prophylactic and abortive treatment of headaches.[17] However, for patients with previous migraines or chronic headaches, other medications may need to be prescribed.[17] Gabapentin, amitriptyline, and nortriptyline are often

prescribed as prophylactic migraine medication and can produce sedation, which can help those suffering from sleep disturbance during post-concussion recovery.[17,27] For sleep disruption, sleep hygiene is first line treatment. Limiting the blue light emitted from computers, phones and TV screens and relaxing mediation are important concepts in sleep hygiene and certainly could help in concussion recovery. Melatonin or other insomnia medications may be prescribed for the patient to get adequate rest to heal.[17]

Acute-onset anxiety or depression often occurs after concussion and there is ample evidence that emotional effects of injury may be a significant factor in recovery.[17] Several studies have shown that selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and tricyclic antidepressants (TCA) may improve depression symptoms after concussion, however it is not known how long medication will be needed or if symptoms will persist.[17,18]

Neurocognitive rehabilitation therapy is another treatment for a more severe brain injury, however empirical investigations to date have not shown conclusive evidence of improving outcome.[18] There are also no published clinical trials of this treatment for mTBI or concussed patients.[18] Previously, therapies for severe injuries concentrated on the stabilization of blood and intracranial pressure (ICP) and generally involved the administration of neuroprotective drugs as well as rehabilitation training.[16] These were mildly responsive and only marginally recoverable after injury.

As concussions continue to be under watchful eyes of parents, families of NFL players, and veterans returning home, treatments are also coming under scrutiny. What these therapies mentioned above do not do, is reverse or slow down the pathophysiology of concussions. That is

the hope for HBOT; to slow down the metabolic imbalance, restore cerebral blood flow and oxygenate the brain well enough that repair mechanisms are functioning efficiently.

Hyperbaric Oxygen Therapy

The idea of hyperbaric oxygen therapy has been around since the 1600s, when a British physician attempted to treat patients in an airtight chamber.[20] There they wanted to cure, patients from Navy, who were suffering from decompression sickness. In 1872, Paul Bert, a French engineer wrote about the physiologic effects of air under increased and decreased atmospheric pressures, beginning hyperbaric medicine as we know it today.[20] The use of HBOT for brain injury pre-dates World War I.[12]

The application of hyperbaric oxygen in treatment of head injuries started in the 1960s with the first study reporting the neuroprotection in experimental brain injured rats, published in 1966 by Choe and Hayes.[22] The primary emergent indication for HBOT is, historically, decompression sickness from gas embolism. It is also most commonly used for acute management of carbon monoxide toxicity, chronic refractory osteomyelitis, radiation injuries to soft tissue, and clostridial myonecrosis.[21]

Today, HBOT is used in five different acute neurological treatments, the best known is for strokes.[12] With so many body systems that HBOT could impact, HBOT should be studied more. With potential benefits of HBOT have been demonstrated in animal models and could impact concussion treatment protocols.[23] Proposed methods in which HBOT works in treatment include stem cell migration, reduced inflammation, alterations in cerebral blood flow, and increased angiogenesis and neurogenesis.[23] Given that the prognosis of concussions and TBI obviously depends on the processes of cell death and survival that happen within the traumatized

tissues, neuroprotective therapies need to improve survival and function within the damaged brain tissue.[21]

There is one absolute contraindication for HBOT in any disease process and that is an untreated pneumothorax.[21] The pressure from the hyperbaric oxygen chamber can cause a life-threating tension pneumothorax very quickly and thus, pneumothoracis should be treated prior to HBOT.[21] Some medications also have a relative contraindication in conjunction with HBOT, in which they cause numerous and diverse complications.[21]

Other respiratory disorders, such as COPD and asthma have been known to cause complications like hypercarbia and pulmonary barotrauma, sequentially.[21] Basic biology would predict that the lung muscle would need to work harder in a hyperbaric oxygen chamber. Those with reduced capacity for air exchange would not be ideal candidates for this treatment. Implanted devices and pumps need to be tested beforehand against the pressure during the procedure.[21] Common sense would expect as with the respiratory disorders, any person using therapies dependent on a certain amount of pressure should not use the chamber treatment option.

Many studies have mentioned relative risks in HBOT that some patients experience including; minor Eustachian tube dysfunction, upper respiratory infections prior to treatment and eye barotrauma.[21] Pregnancy was thought to be a contraindication but new studies have shown that HBOT is indicated in some conditions of pregnancy.[21] Oxygen toxicity has been a known risk, inducing grand mal seizures and some medications and conditions increased the risk.[12]

The indications for HBOT must be weighed against the contraindications. Interprofessional collaboration is critical to safeguard that the patient's contraindications are considered and ruled out while ensuring that HBOT is used with evidence-based medical

decisions.[21] In a literature review, Wang et al. found within 10 studies that severe complications are very rare and mild side effects are easily reversable.[16]

How does hyperbaric oxygen therapy work and what processes does it affect in the body? HBOT uses increased atmospheric pressure and hyperoxia as treatment for disease pathophysiology as defined by researchers.[24] After hemoglobin has become 100% saturated, plasma then can be bound to oxygen molecules, which are more easily used in tissue that has an absence of red blood cells.[25] Furthermore, pressure has a great effect in human tissues that are under tight autoregulation control, such as the brain, where the intracranial pressure is normally 0.0092–0.0197 atm.[26] The exact mechanism of action of HBOT is unknown but speculated to be similar to other mechanisms researched for non-CNS wounds.[12]

Research postulates HBOT employs its wound-healing effects by expression and suppression of oxygen and pressure sensitive genes throughout the body.[12] During animal trials, it was found that the primary gene clusters affected were anti-inflammatory genes and secondly, genes for increased cell growth and proliferation.[12] Cell growth is needed for wound-healing, including contusion of the brain.

It is important to select the appropriate oxygen concentration, oxygen inhalation mode, inhalation time and treatment times based on research's significant findings with different pressures and oxygen settings.[16] Typical HBOT programs use a pressure of 1.5 or 3 atm for consecutive periods lasting 30–90 minutes, repeated multiple times over weeks to months.[16] Increasing the atmospheric pressure by just one half increases the plasma oxygen levels 7 fold or 700%.[27] Since 1 cm^3 of normal brain tissue contains about 1 km of blood vessels, high oxygen supply is crucial for repair of the damaged regions.[28]

Current Research

Animal studies are most commonly performed as pre-clinical studies completed with varying experimental designs and methods. Yet, understanding of HBOT, its benefits and possible side effects, can still be gained from these studies. Previous animal trials that were reviewed in 2016 by Hu et al., show neuroprotective effects in the acute phase directly after a concussion event.[22] In a rat model, a HBOT session 3 hours after impact resulted in decreased apoptosis and reduced secondary brain damage.[22] Reducing apoptosis before damage has been done, should also reduce initial concussions symptoms.

Another model showed inhibition of mitochondrial permeability, making them more stable, and reduced neuroinflammation.[22] HBOT also demonstrated inhibition of gliosis and stimulation of angiogenesis and neurogenesis if started within 3 hours of impact.[22] Animals studies show promising effects, in reducing pathological effects and hopefully are reciprocal to human studies.

These prior results of short term, acute phase concussion established positive effects with HBOT when started within 24 hours of impact.[22] A trauma-associated neurological study in animals showed impairment regressed significantly following 3 weeks of repeated HBOT, a process that is believed to be mediated by distinct remyelination in the ipsilateral injured cortex, as validated by the associated recovery of sensorimotor function.[16]

Current research is split in result findings. Many animal research studies are finding physiological and clinically significant improvements with HBOT, while human research is producing conflicting results. During a multicenter observational study, HBOT had 4 major findings, including; significant improvements in symptoms, cognition, mood, quality of sleep and significant imaging results.[12] This study also had one of the longest follow up periods of any

HBOT study. The results were mirrored in this study by patients who no longer needed psychoactive or narcotic prescriptions to control symptoms.[12]

Tal et al. published a study in 2017 with MRI and DTI analysis that showed marked neurological improvement after HBOT treatments.[19] Fifteen patients were recruited with chronic TBI symptoms and underwent 6 months of HBOT treatments. Table 2 shows pre-treatment neurocognitive function taken through a standardized assessment (NeuroTrax) and post-HBOT neurocognitive scores with mostly significant p-values.[19] Information processing speed had the greatest improvement, along with memory and executive functions, like self-control, self-monitoring and flexible thinking, with a 15% increase in function.[19] Improvements in these areas would make returning to school and working increasingly faster and practical.

Another remarkable finding in this study was seen in the white matter tracking using DT imaging pre and post HBOT.[19] Receiving imaging both before and after therapy will create data that can used to determine significance as well as imaging to visualize neuronal changes. Figure 2 shows fiber numbers increasing in this single patient post-HBOT, suggesting that brain microstructure angiogenesis can be induced by HBOT.[19]

Brain recovery encompassed gray and white matter areas, white matter tracts and angiogenesis, increased cerebral blood flow and improved cognitive functions.[19] Pathophysiology research has unambiguously shown that decreased blood flow following a concussion had large implications in recovery for patients. Angiogenesis of white matter tracts help regenerate lost neuronal tracts and possibly mend areas of instability that patients may face, such as balance, coordination and memory.

DTI imaging, stated above using fractional anisotropy and mean diffusivity, correlated with other research. They found statistically significant increase in FA in motor regions, the

cingulum, and the genu of the corpus callosum.[19] There was also a decrease in MD in the frontal lobe.[17] The increase in FA and decrease in MD post HBOT, together with cognitive function improvement of patients suggest positive findings in HBOT.[19] This study has shown, through multiple imaging, neurocognitive assessments and statistical analysis that for the first time in humans, brain microstructure recovery can be induced by HBOT.[19]

In a comparable study to the previously mentioned, published in 2017, with 154 patients that included a long follow up, patients were exposed to 1.5atm at 100% O_2 for 90 minutes, multiple times a day, for 5 days a week.[26] This study also looked at all severities of head injuries and showed that HBOT improved any severity of injury.[26] This was a new finding with other research stating that only severe injuries may benefit from HBOT. Imaging was done using single photon emission computed tomography (SPECT) and perfusion sequences in MRI, with cognitive studies using NeuroTrax.[26] They found that after the acute insult, HBOT was still effective regardless of the TBI severity.[26] The clinical improvements were well documented by objective computerized neurocognitive tests, with the most significant improvements found in memory, attention and executive function.[26] Objective findings make results clearer and more reliable for decisions about this new therapy.

This is very similar to the previously mentioned study completed by Tal et al. Figure 3 illustrates the finding in a comparison of baseline data and post HBOT. It shows statistically significant improvement in all cognitive domains.[26] In this study, researchers also sought to correlate cognitive changes to metabolic imaging results. They found that there was a significantly larger magnitude of metabolism increase in the anterior cingulate, postcentral cortex and prefrontal area, using SPECT imaging.[26] This relationship gives further strength to the study

results and serves as an excellent tool for gaining better understanding of brain functionality and recovery with HBOT.[26]

There are many veteran based studies being done based on funding through the Department of Defense (DoD) and Veteran Administration (VA). Several studies state that they did not find significant results during clinical trials. One study looked for improvement in post-traumatic stress disorder (PTSD) scores after HBOT.[29] Between pre- and postintervention marks, they revealed no significant differences on individual or total scores in the Posttraumatic Disorder Checklist-Military Version or Rivermead Post concussion Symptom Questionnaire.[29] There are some limitations, to this study that the discussion will explain. Another study demonstrated a successful randomization, however there were no significant main effects for HBO at 1.5 or 2.0 atm equivalent compared with the sham compression.[30] Much research is still to be done with this select group of patients.

Another recent case control study of veterans of the US armed forces with concussions with or without PTSD, found substantial improvements in PTSD symptoms, neurological exam, memory, intelligence quotient, attention, cognition, depression, anxiety, quality of life, and brain blood flow following HBOT.[21] PTSD and PPCS have been new research topics, especially in veterans. This will be another application for HBOT that will possibly positively impact a vast number of patients.

A 2020 study Gwadi hoped to show that normobaric oxygen therapy (NBOT) was as effective as HBOT in reducing mortality and clinical recovery.[21] NBOT means that there is not increased atmospheric pressure being applied and only 100% oxygen. The completed research did find that NBOT was effective in reducing mortality after a concussion but clinical recovery was not significant in this case.[21]

A follow-up study attempted to compare the results of HBOT vs NBOT as well as a standard of care (control group) in the case of severe TBI to see if either would show significant clinical recovery.[21] The study found that HBOT increased cerebral metabolic rate, decreased lactate, decreased ICP and increased cerebral blood flow when compared to NBOT and control groups.[21] Along with these positive result findings, there were no adverse outcomes or harmful effects noted within this study.[21]

There are similar research findings that have been noted in Mozayeni et al. These results underscore the importance of HBOT-induced slowing of cell death within the tissue after concussions.[21] Such mechanisms echo the results and findings of neuroprotection of HBOT seen in brain ischemia and subarachnoid hemorrhage.[21] Subarachnoid Hemorrhage is another research application that should be applied for the benefit of many patients.

Like the previous study, which compared NBOT to HBOT, other researchers proposed a comparison between pre-injury HBOT treatments to "normal" post-injury HBOT. They used adult rats and a repetitive mild concussion focus to study the effects of pre-injury HBOT.[25] They found that HBOT pre-injury could have a neuroprotective action with cerebral anerobic metabolism being at its highest.[25] Figure 4 shows MRI images of rat brains and the areas that have healed and been reduced in both pre and post HBOT in concussed rats.[25] Gonzales-Portillo et al. also found similar results, namely, when primary neuronal cells were subjected to HBOT preconditioning before an insult, there was a lesser number of cell deaths.[2]

Results

These discoveries form the possibility of an HBOT treatment for individuals at a high risk of disability by providing a way to reduce secondary cell death.[2] Significant P-values and MRI scans have been provided in the appendix to show objective findings in HBOT trials. This

paper has presented a limited range of data; however, several conclusions and recommendations can be made from it.

Discussion

Interpretations

Most of the findings reviewed revealed a significantly positive effect of HBOT in treating concussions and TBIs. Research exposed some key physiological pathways that have been at work for many decades. There were significant improvements and an important number of advances in all outcome instruments; symptoms, cognition, mood, quality of life, and imaging that were reproducible across studies and strengthened by P values.[22,28] Animal trials showed HBOT effective in acute and chronic settings as well as full scope analysis of neuronal tissues.[16,22] With the help of animal trials, the pathophysiology was better understood. Researchers could see increased angiogenesis, neurogenesis, mitochondrial activity, cerebral blood flow and remyelination of white matter tracts.[9,18,19] There was evidence of hyperoxia significantly improving animal outcomes by simply reducing mortality.[23] Expanding on the original model, various methods were used to induce a concussion with HBOT as the treatment, at various settings, and all were found to have successful animal trials.

When human trials were underway, the physiological affects against recovered sensorimotor function could be synthesized.[17,26,28] SPECT imaging and objective cognitive scores, using NeuroTrax analysis, gained the best results that were objective and unbiased.[17,26,28] Furthermore, post-treatment brain SPECTs revealed an anatomical–functional relationship in regard to HBOT's effect on neuroplasticity.[26] They found that when studies completed long term follow up, 90% had improved symptoms 6 months after therapy.[12,26] Even further follow up on

studies would be suitable to know the long term extent of HBOT. This research could lead to better protocols and knowledge about the effects of HBOT.

When comparing physiological parameters and neurological function scores between control and treatment groups, HBOT is effective in all severities of concussions and improves patients' prognosis and potentially erases long term disability.[16] The common denominator underlying all these mechanisms is that they are oxygen dependent and consequently HBOT may enable the metabolic change simply by supplying the missing energy/oxygen needed for these regeneration processes.[26] It has been know, that oxygen is not only a vital element but can also be used as a drug is pathological processes. Researchers also found that when patients, or animals, were pretreated with HBOT their healing process was exceptionally faster and showed neuroprotection before injury even happened.[2,25] The exact mechanism is not known, but hypothesized that oxygen sensitive genes may be upregulated prior to injury, and thus be more efficient.

Six different studies found that even though some mild side effects and complications have occurred, such as earaches, headache or chest pain, these self-limiting symptoms are ostensibly reversible.[16] These side effects may warrant further follow up in case the brain is not the only part of the body that was injured during the brain-trauma inducing event. However, HBOT can be considered safe when treating concussions and TBIs'.[16] Translational research of HBOT in a variety of TBI models mentioned in this paper have shown neuroprotective effects.[25] Due to the heterogeneity of human concussion and symptom reporting, the efficacy of clinical HBOT and an optimal regimen for HBOT remains elusive for now.[25]

Implications

TBI is common both within the general population and also within the active military, particularly due to their exposure to improvised explosive devices. Current treatments are not ideal and include off-label use of black box labeled psychoactive medications, which may contribute to the already high rates of suicidality among this population.[23] Finding a new solution for soldiers returning from war other than medication, would help save our healthcare system billions each year.[27]

The implications for sports aged kids and adults would mean that the lasting sequela of multiple concussion need not follow them indefinitely. With chronic traumatic encephalopathy (CTE) being identified in 2005, parents are increasingly worried about letting their kids play contact sports. As much as parents want to protect their kids, sports are not the only thing that can disrupt a person's life. Everyday accidents happen and a treatment that can reverse the trauma would be life-altering for these patients.

Limitations

Some limitations found through examining hyperbaric literature include; small cohort sizes, subjective questionnaires and limited clinical trials. Research weaknesses like subjective questionnaires can be overcome by using NeuroTrax, as presented in multiple papers, an objective measurement of cognitive symptoms. Hadanny and Stoller believe that military clinical trials are skewed due to their use of subjective questionnaires and the possibility of false data due to secondary gain from those service members.[25,26] Small cohort sizes may be redeemable, by longer trial acquisition times and with research showing that HBOT is effective in chronic stages of injury, a large cohort is attainable. The small number of clinical trials is both a test of time and possibly a look into patent policies.[27]

HBOT in the treatment of concussions is a relatively new therapy. With the uptick in concussion reporting, it is possible that the number of clinical trials will continue to grow. Stoller believes that due to HBOT not being a patentable procedure, there are less companies that want to invest in this research. Whether or not this is true, the DoD has put much time and resources into finding alternate treatments for many of their wounded soldiers.[12] The scientific community finds limitations in studies that do not have placebo effects. However, Boussi-Gross et al. explains that when the treatment raises atmospheric pressure about 1.3atm, the patient can feel the difference, therefore making a sham control very difficult to model.[11] When studies include the sham effect, it was found that the results were less significant due to sham groups having improved SPECT imaging and better neurological function even without prior injury.[11] Research has shown that this should be true as oxygen is a drug. Increased oxygen at any setting, induces reparative genes in all body systems.[28]

Recommendations

Further research with critically driven, strong methodological procedures that include multiple comparator arms are needed to ascertain conclusions and to make recommendations in the risk/benefit ranges for HBOT versus "standard care."[30] With standard of care protocol potentially including, psychoactive drugs that impair the brain further, rather than working to rebuild its neuronal structure from the inside. We know that drugs may modulate and affect the brain, but the better solution would be to physically change the brain and make it healthier. While long-term data is still lacking, considering the high safety report of the treatment, these results are promising and should encourage rehabilitation centers to consider HBOT for patients with chronic neurocognitive deficits.[26] Future studies should monitor these patients in the long term follow ups, 6 months, 12 months, as well as in their return to activities of daily living.[26]

Quality of life and ability to maintain activities of daily living are main goals for clinicians. Shytle also believes that future trials should measure patient-specific outcomes rather than general overall disease measurements to help further reveal the benefits of HBOT.[23] This will be harder to objectify, but may help gain support in the medical community.

Conclusion

Clinician understanding of the pathophysiology of concussion has expanded significantly over the last few decades. Many of the acute physiological changes, that happen during brain trauma, have received additional support in representations of TBI and with the use of advanced noninvasive neuroimaging, the contributions of oxidative stress, impaired axonal transport and altered neurotransmission are now clearly linked to the initial ionic fluxes, indiscriminate glutamate release and metabolic uncoupling.[4] Additionally, it is progressively possible to see links between the pathophysiology of concussion and the early clinical signs and symptoms.[4] Linking what we can see to what we cannot see going on in the brain is an important stride in attaining evidence-based medical recommendations.

With this better understanding, treatments like HBOT can be refined to fit the physiological process, much like we do with medications. It is believed that HBOT is going to be increasingly accepted by patients and approved by clinicians and subsequently then insurance.[16] Apart from TBI, other cerebrovascular diseases, like subarachnoid hemorrhage, intracerebral hemorrhage and ischemic stroke, also have substantial therapeutical indications to improve prognosis and chronic disease.[18]

When HBOT interventions under specific conditions are applied properly, only a few major adverse events have been observed and then only very rarely, such as pulmonary barotrauma, pulmonary edema and seizures.[2] Based on these limited studies, it is clear, that

HBOT could be an effective therapy for traumatic brain injuries and concussions. HBOT stimulates brain "functions", such as cerebral metabolism and blood flow. However, additional studies are needed not only during the acute phase of the injury, but also long-term studies evaluating outcomes to determine how HBOT is beneficial to patients.[25] If HBOT is successful in treating brain trauma, it may also prove effective to prevent, detect, treat or manage other illness.

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Appendix

Figure 1 [15]

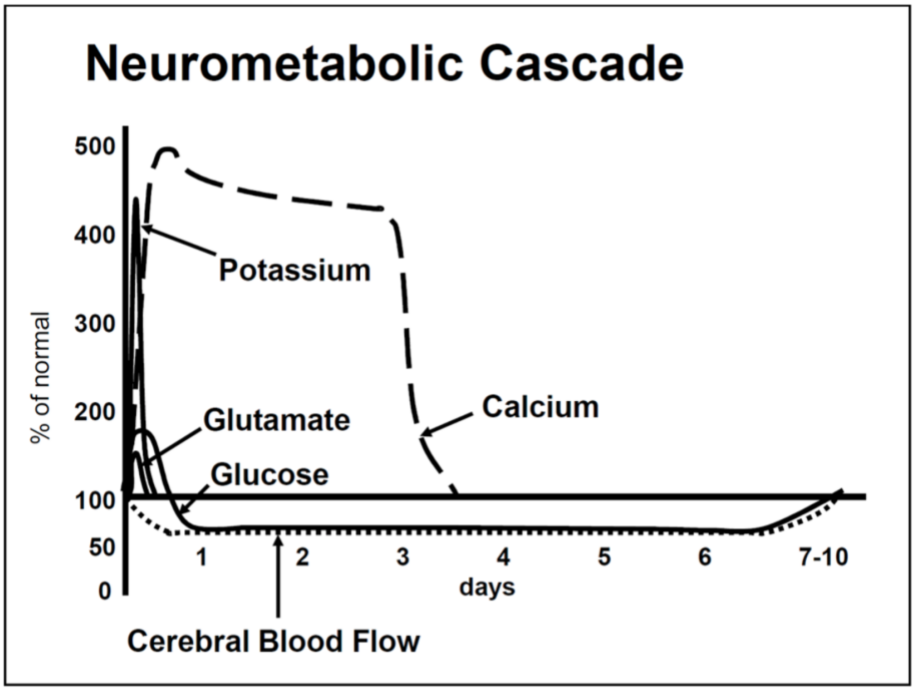

Figure 1.
Time course of the neurometabolic cascade of concussion.

Table 1. [17]

TABLE 1

Signs and symptoms of concussion

Symptoms
Headache
Dizziness
Balance problems
Unsteadiness
Light sensitivity
Vision changes
Nausea
Drowsiness
Amnesia
Sensitivity to noise
Tinnitus
Irritability
Feeling slowed down or "in a fog"
Difficulty concentrating
Difficulty remembering
Low energy, drowsiness
Sleep disturbance
Increased emotionality
Signs
Loss of consciousness
Amnesia
Confusion
Disorientation
Appearing dazed
Eye-movement abnormality
Inappropriate emotionality
Physical incoordination
Imbalance
Seizure
Slowed verbal responses

Table 2 [19]

TABLE 2 | Cognitive indices at baseline, and after Hyperbaric Oxygen Therapy (HBOT).

	Baseline	Post HBOT	Mean change	Sig.	Sig. with time as covariate
Global	88.2 ± 2.5	96.4 ± 2.5	8.2 ± 1.5	***0.0001**	**0.0004**
Memory	82.2 ± 5.3	92.7 ± 4.7	10.5 ± 2.4	***0.001**	**0.008**
Executive Functions	83.9 ± 3.8	95.2 ± 3.4	11.3 ± 2.7	***0.001**	**0.002**
Attention	88.1 ± 3.5	96.3 ± 2.9	8.2 ± 4.0	0.062	0.105
IPS	84.3 ± 3.3	97.4 ± 3.8	13.1 ± 2.7	***0.0001**	**0.001**
VSP	96.6 ± 4.0	105.3 ± 3.1	8.7 ± 3.0	***0.01**	**0.04**
Motor skills	92.3 ± 4.1	98.2 ± 3.8	5.8 ± 2.0	***0.0009 (W)**	

Data are expressed as means ± standard errors. IPS, Information processing speed; VSP, Visual spatial processing; W, Wilcoxon signed-rank test. Bold values indicated statistically significant $p < 0.05$.

Figure 2 [19]

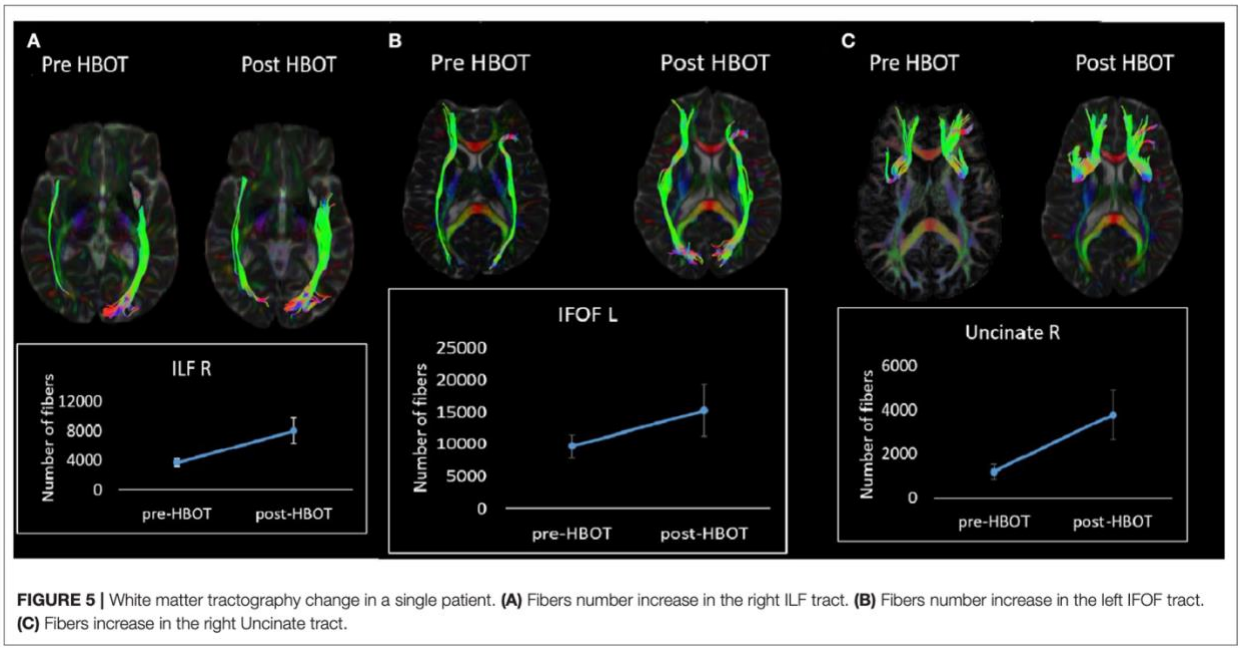

FIGURE 5 | White matter tractography change in a single patient. **(A)** Fibers number increase in the right ILF tract. **(B)** Fibers number increase in the left IFOF tract. **(C)** Fibers increase in the right Uncinate tract.

Figure 3 [26]

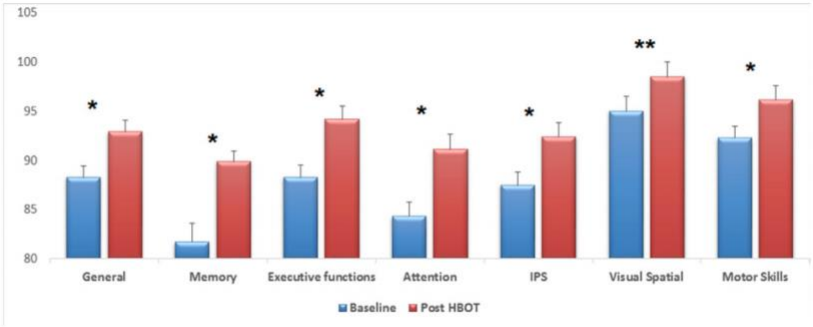

Figure 3 Mean changes of post-HBOT compared with pre-HBOT for the entire cohort. After HBOT, all cognitive domains improved significantly, with the most striking changes seen in memory and attention. *P<0.0001, **p=0.005, HBOT, hyperbaric oxygen therapy; IPS, information processing speed.

Figure 4 [25]

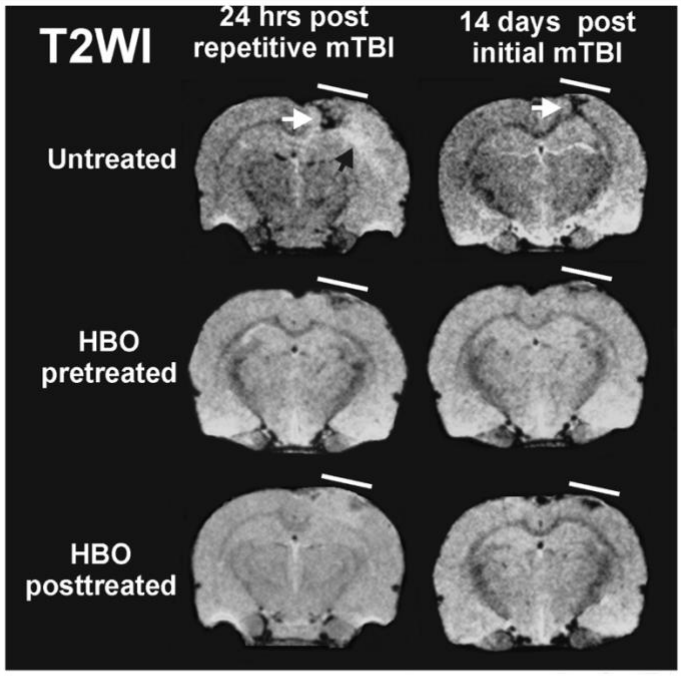

Figure 1 HBO reduces rmTBI lesion volumes. Pre- and post-treatment with HBO reduces lesion volume identified from magnetic resonance imaging (MRI, T2 weighted images). Repetitive mild traumatic brain injury (rmTBI) was induced 3 days apart and resulted in ipsilateral tissue damage. On T2WI, hypointensities (white arrow) are consistent with bleeding while hyperintensities (black arrow) suggest edema formation. At 24 hrs after the rmTBI, HBO pre- or post-treatment significantly reduced the lesion size compared to untreated animals. The neuroprotective effects persisted to 14 days after the initial mTBI.

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