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Hyperbaric Oxygen: Mechanisms and Innovations in the Management of Post-Concussion Syndrome

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Abstract

Hyperbaric Oxygen Therapy (HBOT), the use of pure oxygen (100% O_2) at high pressure (2–3 ATM), is gaining prominence as a tool for managing persistent post-concussive symptoms, otherwise known as post-concussion syndrome (PCS). Recent research has emerged that elucidates the mechanisms by which HBOT improves PCS. This article reviews the progression and pathophysiology of PCS, challenges in diagnosis, and novel imaging solutions. It also delves into recent advancements in the understanding of HBOT mechanisms and the benefits observed from HBOT in PCS patients. The discussion concludes with an examination of innovative imaging techniques, novel biomarkers, the potential role of data sharing, machine learning, and how these developments can advance the use of HBOT in the management of PCS.

Keywords: hyperbaric oxygen, mild traumatic brain injury, concussion, post-concussion syndrome, postconcussional syndrome, persistent post-concussive symptoms, mild neurocognitive defect, ischemia, diffusion tensor imaging, diffusion weighted imaging, MRI, SPECT, BOLD, machine learning, biomarkers

1. Introduction

Concussions, also known as mild traumatic brain injuries (mTBI), have become the subject of intense research in recent years. As more light is shed on the debilitating long-term consequences of mTBI, increased emphasis is rightfully placed on prevention, accurate diagnosis, and treatment modalities among clinicians and other health professionals. mTBI can present with a wide variety of symptoms; the most common acute symptoms being headache, dizziness, imbalance, fatigue, and cognitive impairment. As acute symptoms subside, long-term manifestations include a variety of somatic, emotional, and cognitive symptoms [1]. Loss of consciousness immediately after injury and/or post-traumatic amnesia are also seen in cases of acute mTBI [2]. Non-resolution of these symptoms within the expected timeframe can be indicative of post-concussion syndrome (PCS). The 6th International Conference on Concussion in Sport (2022) in Amsterdam describes "persistent" symptoms of concussion as those lasting longer than 4 weeks in children, adolescents, and adults [3, 4]. This builds upon the definition set forth by the 5th International Conference on Concussion in Sport (2017), which defined PCS as sequelae of mTBI without resolution of symptoms within weeks or months, and with refractory symptoms not better explained by another etiology [5]. Patients with PCS suffer from headaches, dizziness, neuropsychiatric symptoms such as depression, and continued cognitive impairment [6]. As its symptoms are non-specific, accurate diagnosis and treatment for patients with PCS remains a challenge. Furthermore, the pathogenesis of PCS is still only partially understood. Given the long-term consequences of mTBI, improved diagnostic and neuroimaging techniques will be of vital importance to better elucidate the pathology of PCS and develop effective treatments.

Hyperbaric oxygen therapy (HBOT) involves the administration of pure oxygen (100% O_2) in a highly pressurized chamber at 2–3 atmospheres (atm) [7]. HBOT has long been indicated for several pathologies such as dermal burns, carbon monoxide poisoning, and decompression sickness; however, its use in the management of mTBI and PCS is a more recent phenomenon. Though an emerging body of studies suggests HBOT carries advantageous effects, a significant gap exists in comprehending the intricate mechanisms through which these benefits are conferred. Existing investigations predominantly revolve around the identification of HBOT biomarkers using innovative imaging techniques. As these mechanisms are further elucidated, HBOT may begin to see even greater usage in the treatment of PCS. Clinical research is also being undertaken to track patients' cognitive outcomes and quality of life following mTBI and HBOT. If data sharing and machine learning are applied to emerging clinical data, novel imaging, and newfound biomarkers, clinicians may be better informed in their use of HBOT as a management strategy for PCS.

This review begins with a discussion on PCS, including its epidemiology, natural history, treatment, current barriers to accurate diagnosis, and novel diagnostic approaches. This is followed by a synthesis of the presently understood mechanisms of HBOT, an exploration of novel imaging techniques used to capture relevant biomarkers, and a concluding discussion on machine learning and its potential role in informing the clinical use of HBOT.

2. *Post-Concussion Syndrome: Current Understanding*

2.1. Epidemiology and etiology

Concussions are relatively common in the United States, with over 3.8 million reported cases each year [8]. Prevalent causes include falls, motor vehicle accidents and contact sports-related injuries [9]. Nearly 80% of these are classified as "mild" and only 20–25% require hospitalization [10]. However, assessing the incidence of mTBI is difficult for a variety of reasons, and the true number sustained each year is likely to be much higher than data suggest. Many cases of mTBI go undiagnosed because patients fail to seek medical care following injury [11, 12]. Also, the myriad of symptoms with which concussions may present may also cause mTBI misdiagnosis. Symptoms such as headache, nausea, and dizziness are non-specific, thus both patients and providers may not necessarily attribute them to a concussion. Conflicting data exist for the prevalence of PCS. Some reports indicate that nearly 30% of patients with mTBI will go on to develop PCS, while others estimate that the number could be as high as 80% [13]. Identifying reliable risk factors to identify patients who will develop PCS has also proven challenging for clinicians. In addition to prior mTBI, data suggest premorbid physical limitations, neurologic disease, life stressors, student status, and old age are potential risk factors [14]. Additionally, some studies have shown female sex to be a predictor of greater risk [15], with older women bearing the highest risk for long-term mTBI sequelae [16]. In one study examining adolescent athletes who sustained first-time sports-related concussions, females were found to be symptomatic for a significantly longer period than their male counterparts [17]. The most reliable predictors of future PCS development seem to be related to either previous concussion status or specific symptom presentation at the time of injury. For example, in a study among athletes experiencing concussions, researchers assessed several risk factors including sex of the patient, family history of concussions, previous treatment of headaches, and patient reported Post-Concussion Symptom Scale (PCSS) [18]. PCSS is a measurement of symptom burden derived by the addition of patient reported ratings on the severity of common concussion symptoms. In their assessment, the only measurement with significant predictive value was higher PCSS score, but even this was just mildly predictive (odds ratio: 1.04–1.08). Other tools used in the

assessment of PCS include the Sport Concussion Assessment Tool (SCAT), Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), and Vestibular/Ocular Motor Screening (VOMS). The SCAT was designed as a tool to assess athletes on the sidelines of sporting events by coaches, trainers, and medical professionals. The most recent iteration, SCAT6, comprises a symptom assessment, cognitive evaluation, neurological screening, and balance test. Its intended use is to assess mTBI in the acute phase of injury and its benefit is limited to 7 days following injury [19]. As such, its use in the evaluation of PCS should only be considered within that timeframe. ImPACT is a tool that measures various aspects of cognitive function, including memory, reaction time, speed of cognitive processing, and concentration. Though it was widely used in the early 2000's, its performance has recently been brought into question due to issues regarding its embedded validity detector [20, 21]. The VOMS assessment includes testing for smooth pursuit or tracking of objects, horizontal and vertical saccades, near point of convergence, horizontal and vertical vestibular ocular reflex, and visual motion sensitivity. Since these functions can be compromised following a concussion, persistent issues in these domains, particularly if accompanied by provoked symptoms like headache, nausea, or dizziness during the VOMS test, may suggest the presence of PCS. Though these tools have demonstrated some clinical utility in diagnosing concussion, the within-patient test-retest variability has been high resulting in poor reliability [22]. In other studies, it has been postulated that the presence of particular symptoms can be associated with PCS development. Lau *et al.* found that among common symptoms of concussion such as confusion, loss of consciousness, imbalance, fatigue, dizziness, vomiting, and sensitivity to light; only dizziness had a statistically significant predictive value for protracted concussion recovery [23]. Yang *et al.* also found dizziness to adversely affect clinical outcomes during both early and late stages of disease recovery [2]. In patients presenting to ER following concussion, symptoms such as nausea, dizziness, and headache were found to be correlated with more severe post-traumatic complaints six months following injury [24]. Taken together, these studies elucidates the current understanding regarding the the epidemiology and etiology of PCS.

2.2. Pathophysiology

More complete knowledge of the pathophysiology of PCS will be paramount to the development of improved diagnostic techniques and treatments [25–28]. While the precise mechanisms behind PCS remain elusive, it is believed to stem from the ongoing processes associated with the pathogenesis of mTBI, a phenomenon that has been better characterized. Though not intended to be a comprehensive review of mTBI pathogenesis, a brief overview of currently proposed pathways in the literature will be important to understanding both current and future diagnostic

techniques, criteria, and the potential of HBOT [29]. A more in-depth mechanistic explanation of concussion pathophysiology has been outlined in several reviews published by Giza *et al.* [30–32].

Any impact that causes sufficient deceleration of the brain can result in dysregulated neurometabolism following injury. Biomechanical insult to the brain induces unregulated glutamate and gamma-aminobutyric acid (GABA) release with concurrent potassium, calcium, and sodium influx, thereby leading to increased ionic disequilibrium [30–33]. Neurons subsequently upregulate activity of adenosine triphosphate (ATP) dependent sodium-potassium pumps to restore ionic balance. As consumption of ATP rises, cerebral glucose metabolism spikes to meet increased cerebral energy demands [30]. This reaction represents a short phase of cerebral hyperglycolysis accompanied by comparatively low oxygen use [34]. Concomitantly, cerebral blood flow (CBF) increases in the acute phase, which may be explained by neurovascular coupling and functional hyperemia [35, 36]. Following acute increase, CBF subsequently decreases to below pre-injury levels for up to 14 days [37]. Thus, metabolic demand of brain parenchyma increases while simultaneously, the required blood flow to meet that demand decreases—an event deemed "metabolic crisis" [31, 32, 38]. This may explain why cerebral ischemia has been observed up to 10 days following mTBI [39]. Overall, the resultant decreased brain tissue partial oxygen pressure following mTBI has been associated with poor cognitive function when assessed by the Glasgow Coma Score (GCS) [40].

In contrast, improved outcomes have been reported when hypoxia is avoided through neuromonitoring [41–43]. Abnormalities in tissue respiration and mitochondrial inefficiency have also been examined. Oxygen extraction fraction measures the amount of oxygen a tissue uses compared to the total oxygen delivered and is one metric used to evaluate the efficiency of cerebral metabolism. A decreased oxygen extraction fraction is seen in the acute phase of TBI patients, which can be interpreted as acutely increased CBF and decreased oxygen usage. This would indicate that inefficient mitochondrial function may be an important underlying pathophysiological factor [34, 44]. Mitochondrial dysfunction could be partially explained by the increased influx of calcium via glutamate binding to *N*-methyl-D-aspartate (NMDA) receptors [45]. Increased mitochondrial calcium concentrations decreases rates of oxidative phosphorylation, thereby exacerbating metabolic insufficiency [30].

Elevated intracellular calcium concentration also predisposes the brain to further injury. Injurious forces may cause axons, dendrites, and astrocytes to sustain mechanical damage. The resulting calcium influx causes release of mitochondrial cytochrome c and activation of proteases which degrade cytoskeleton structures [46]. Neuronal stretch may cause microtubule damage affecting both the cytoskeleton and axonal synapse, whereby neuro-transmission may be

diminished [47, 48]. Structural weakening of the axon cytoskeleton may partially explain the vulnerability to a second concussive injury [49, 50]. Collectively, pathologic alterations to cerebral metabolism, cytoskeletal integrity, neurotransmitter release, CBF, and oxygen utilization, are all likely contribute to PCS pathophysiology.

2.3. Current management protocol

Typically, patients with concussions will see the resolution of symptoms within weeks of sustaining the injury. Symptom burden is generally high in the first 7–10 days [51]. In 15% of cases, patients continue to exhibit symptoms after one year [52]. Treating patients suffering from PCS generally involves managing symptoms as they arise. In patients who have prolonged symptoms, early exercise is associated with faster recovery [53]. Though some studies suggest that high levels of physical and cognitive activity may prolong symptoms [54], newer data suggest that sub-symptomatic moderate aerobic activity beginning 48 h after injury significantly decreases recovery time [55, 56]. This is in accordance with previous studies suggesting that patients who have prolonged symptoms benefit from aerobic exercise [57]. Other treatment modalities for mTBI and PCS include physical therapy, cognitive behavioral therapy, vestibular therapy, visual therapy, and pharmacologic management [58]. As contemporary breakthroughs continue to advance the current understanding of the underlying pathophysiology, additional evidence-based treatment modalities are expected to emerge.

3. Diagnosing post-concussion syndrome

3.1. Diagnostic criteria

To accurately assess PCS, it is vitally important to first understand the patient's original TBI presentation. If the diagnosing clinician performed the initial evaluation when the patient first presented with concussion symptoms, this can make the future monitoring process for PCS more straightforward. First, the severity of brain injury must be characterized. As such, a detailed history of the event from either the patient or bystanders can be particularly useful to understand the complete clinical picture. Several screening tests exist to evaluate the severity of concussions, some of which have predictive value for PCS development. To qualify for diagnosis of mild TBI, patients should not experience more than 30 minutes of loss of consciousness nor more than 24 hours of post-traumatic amnesia [59]. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) states that for a diagnosis of PCS to be made, there must be evidence of head trauma that is "sufficiently severe to result in loss of consciousness" [60]. Mental status must also be altered, and symptoms may present

Table 1. Varying PCS diagnostic criteria based on four primary sources.

Source	DSM-IV	DSM-V	ICD-10	5th International Conference on Concussion in Sport
Diagnostic criteria	History of TBI causing "significant cerebral concussion" Cognitive impairment in attention or memory Presence of at least three of the following: fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, personality change, apathy, appearing shortly after injury and persisting for at least 3 months Symptoms begin after injury or represent significant worsening of pre-existing conditions Symptoms are not better explained by another etiology	History of head trauma Presence of at least one of the following: loss of consciousness, posttraumatic amnesia, disorientation, or focal neurological signs such as hemiparesis or abnormal neuroimaging	History of head trauma Onset of symptoms within 4 weeks of injury Presence of at least 3 of the following: headache, dizziness, fatigue, noise intolerance, irritability, emotional lability, depression and/or anxiety, subjective complainants of difficulty in concentration and memory problems No specification of symptom duration for diagnosis of PCS	History of concussion Symptoms do not resolve within typical timeframe (10–14 days for adults, 4 weeks for children) Symptoms not better explained by another etiology

anytime within 4 weeks following injury. The ICD-10 does not specify a minimum duration of symptoms to qualify as PCS, and no objective findings are required to make a diagnosis [13]. In comparison, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) refers to PCS as "Major or Mild Neurocognitive Disorder Due to Traumatic Brain Injury" and requires head trauma for a diagnosis [61]. However, the DSM-V makes no requirement for loss of consciousness and stipulates that symptoms must begin either immediately before unconsciousness or immediately after consciousness is regained. In the DSM-IV, the criteria for a diagnosis of postconcussional disorder is defined as having "a history of head trauma causing significant cerebral concussion," "evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention," and "three or more of the following symptoms lasting at least three months; fatigue, disordered sleep, headache, vertigo or dizziness, irritability, anxiety or depression, personality change, or apathy [62]." Finally, the consensus statement on concussions made during the 5th International Conference on Concussion in Sport (2016) also stipulated that head trauma must be present with no requirement for loss of consciousness [5]. A summary of these varying criteria is presented in Table 1. If a diagnosis of concussion is made, clinicians should be vigilant in monitoring patients throughout the recovery phase. These varying diagnostic criteria, including their inconsistency regarding radiographic abnormalities and the non-specific PCS symptomatology, underscore the need for further clarity.

Such limitations are likewise evident in the great disparity of diagnostic criteria used clinically. For example, in a 2015 study by Rose *et al.* of nearly 600 physicians, 26.6% required PCS symptom duration for less than two weeks, 20.4% for two to four weeks, 33% for one to three months, and 11.1% greater than three months before diagnosis [63]. This is not surprising as the knowledge of the clinical presentation or pathophysiology of PCS to develop a consensus criterion for diagnosis is still insufficient. As research in this topic continues, consistent biomarkers, improved neuroimaging techniques, and universally agreed-upon diagnostic criteria will greatly aid the accurate diagnosis and management of post-concussion sequelae.

3.2. Current tests for PCS

The American Academy of Neurology (AAN) includes the following in its guidelines for the evaluation of concussion: Post-Concussion Symptom Scale (PCSS), Graded Symptom Checklist, Standardized Assessment of Concussion (SAC), Balance Error Scoring System (BESS), Sensory Organization Test (SOT), and formal neuropsychological testing [13]. These are useful for evaluating concussion symptoms acutely. However, tests like SAC and BESS are generally not viable screening tests beyond one-week post-injury [5]. PCSS can help predict which patients are at higher risk for prolonged symptoms. This is demonstrated by Meehan *et al.*, who showed higher PCSS scores to be the only independent variable among sex, age, loss of consciousness, and amnesia at time of injury to be associated with prolonged concussion symptoms [64]. In a separate study, 85% of pediatric patients with a PCSS score <13 had symptoms resolved within 28 days of injury [18], further underscoring the usefulness of the PCSS system for evaluation of patients at high risk for post-concussion syndrome.

Another useful metric involves neuropsychological testing and its capacity to evaluate cognitive function. As working memory, processing time, and reaction time are particularly vulnerable to impairment following TBI, deficits in these functions are typically assessed [65]. It is important to note again that symptoms of PCS are non-specific, and the results of neuropsychological testing can assist in diagnosing other disorders that can better explain the clinical presentation. As mentioned previously, one of the great challenges of PCS diagnosis is the non-specific nature of its symptoms. Though there is not an official consensus criterion among physicians regarding diagnosis, understanding the currently available tests and how different authorities define PCS can provide a general framework.

3.3. Current imaging techniques

As part of a diagnostic work-up, neuroimaging should be used to eliminate more severe pathology. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are the most used imaging tools in this assessment. In most patients

with mild TBI, CT and MRI show no abnormal imaging. In fact, only 10% of patients with mild TBI will have abnormal CT scan findings [59]. However, in patients with more severe injury, abnormal neuroimaging findings can be relatively more common. GCS is used to determine the state of altered consciousness of patients. A score of 15 is reflective of higher cognitive function, with 0 indicating maximum impairment of consciousness. mTBI is characterized by a GCS of 13–15, while patients with more severe TBI score 12 and lower. Borg *et al.* showed that in patients presenting to hospital with a GCS of 15, only 5% had abnormal intracranial CT findings. Patients with a GCS of 14 showed abnormalities in 20% of scans, while those with a GCS of 13 had abnormalities in 30% or more CT scans [59]. In the setting of TBI, MRI is a more sensitive imaging study than standard CT. In approximately 30% of patients with mTBI and normal CT scan findings, MRI showed white matter lesions consistent with diffuse axonal injury [66].

4. HBOT: observed benefits and emerging mechanisms

4.1. HBOT technique and mechanism of hyperoxygenation

The presumed benefit of HBOT lies in its ability to increase blood oxygen concentration [67]. According to Henry's Law, the amount of ideal gas dissolved in a solution is directly proportional to its partial pressure. Thus, at normal atmospheric pressure (1.0 atm and 21% O_2), the concentration of oxygen in blood plasma is approximately 0.3 mL/dL. Administration of 100% oxygen can increase this concentration to roughly 1.5 mL/dL. HBOT typically involves the administration of pressurized oxygen at 2.5–3.0 atm. At these pressures, the oxygen concentration in blood plasma can reach levels up to 6.0 mL/dL [68]. A recent randomized control trial studying the effects of HBOT on PCS recovery provides a treatment regimen example. Researchers performed 5 sessions of HBOT for 60 min each over 8 weeks, for a total of 40 sessions. Patients assigned to the HBOT arm of the study showed significant improvement over the control group [69].

4.2. Observed benefit of HBOT on PCS

Despite an incomplete understanding regarding the pathophysiology of PCS, HBOT has been observed to benefit both adult and pediatric patient populations. In this section, some of the more prominent analyses on this topic are described with a list of additional relevant studies provided in Table 2.

Example 1: A retrospective analysis

In one retrospective analysis, 154 civilian patients were evaluated before and after HBOT [70]. Using computer generated cognitive tests, metrics such as verbal memory, non-verbal memory, Stroop interference, problem solving, verbal function,

Table 2. Studies examining benefit of HBOT therapy on PCS patients. Methods have been evaluated and studies filtered to include mTBI patients suffering from symptoms greater than 3 months in duration.

Study	Authors	Experimental subjects	HBOT details	Outcome
Hyperbaric oxygen therapy in children with post-concussion syndrome improves cognitive and behavioral function: a randomized controlled trial.	Hadanny A, Catalogna M, Yaniv S, Stolar O, Rothstein L, Shabi A, Suzin G, Sasson E, Lang E, Finci S, Polak N, Fishlev G, Harpaz RT, Adler M, Goldman RE, Zemel Y, Bechor Y, Efrati S.	15 children aged 8–15 with PCS	60 sessions (5 sessions/wk for 3 months) 100% O_2 at 1.5 ATA for 60 min	Significant improvement in: • Cognition (p = 0.01) • Memory (p = 0.02) • Emotion (p = 0.04) • Hyperactivity (p = 0.03) • Planning and organizing (p = 0.007)
Hyperbaric oxygen therapy compared to pharmacological intervention in fibromyalgia patients following traumatic brain injury: A randomized, controlled trial.	Ablin JN, Lang E, Catalogna M, Aloush V, Hadanny A, Doenyas-Barak K, *et al.*	Adults with TBI-related fibromyalgia	60 sessions (daily) 100% O_2 at 2 ATA for 90 min	Significant improvement in: • Pain intensity (p = 0.001) • Quality of life • Pain thresholds Even when compared to traditional pharmacological therapy.
Hyperbaric oxygen therapy promotes consciousness, cognitive function, and prognosis recovery in patients following traumatic brain injury through various pathways.	Chen Y, Wang L, You W, Huang F, Jiang Y, Sun L, *et al.*	44 patients with prior diagnosis of TBI	20 sessions 100% O_2 at 2 ATA for 60 min	Significant improvement in: • Cognitive function impairment • Various TBI severity biomarkers (neuron-specific enolase, S100 calcium-binding protein beta, glial fibrillary acidic protein, brain-derived neurotrophic factor, nerve growth factor, vascular endothelial growth factor)
Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis.	Hadanny A, Abbott S, Suzin G, Bechor Y, Efrati S.	154 patients with chronic neurocognitive damage due to TBI, assessed 0.3–33 years post TBI.	40–70 sessions (daily) 100% O_2 at 1.5–2 ATA for 60–90 min	Significant improvement in: • Cognitive scores (p < 0.00001) • Memory index (p < 0.00001) • Attention (p < 0.0001)

Table 2. (Continued)

Study	Authors	Experimental subjects	HBOT details	Outcome
Hyperbaric oxygen and outcomes following the brain injury: a systematic review.	Iqbal J, Naeem A, Jahangir K, Ali Y, Mashkoor Y, Ashraf A, Mehmood D, Mehmood M, Brandon LW.	1067 patients across 15 studies, 21 of which had severe neurological impairment	Systematic Review: Various HBO_2 Treatments	Fifteen studies were included in this review to assess the safety of HBOT in TBI. Most studies endorsed the effectiveness of HBOT after brain hemorrhage.
Use of hyperbaric oxygen in traumatic brain injury: retrospective analysis of data of 20 patients treated at a tertiary care centre.	Sahni T, Jain M, Prasad R, Sogani SK, Singh VP.	20 patients with TBI (retrospective analysis)	30 sessions	Showed improvement in cognitive functions
Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury—randomized prospective trial.	Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, Friedman M, Hoofien D, Shlamkovitch N, Ben-Jacob E, Efrati S.	56 mTBI patients with PCS	40 sessions (5 days/wk) 100% O_2 at 1.5 ATA for 60 min	40 sessions of HBOT were administered to patients with prolonged PCS, and yielded significant improvement in cognitive function and quality of life. The control showed no significant improvement of either.
Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial.	Harch PG, Andrews SR, Rowe CJ, Lischka JR, Townsend MH, Yu Q, Mercante DE.	63 patients with PCS	40 sessions (daily) 150 kPa for 60 min	Significant improvement in: • Neurobehavioral symptoms • Depression • Anxiety • Sleep • Quality of life Control subjects who were administered HBOT after a waiting period of no therapy also yielded similar results.
Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes.	Cifu DX, Walker WC, West SL, Hart BB, Franke LM, Sima A, Graham CW, Carne W.	61 male marines with combat-related PCS	40 sessions (daily) 100% O_2 at 1.5 ATA for 60 min, OR 100% O_2 at 2.0 ATA for 60 min	There was no significant improvement associated with HBOT specific to combat-related PCS.
Hyperbaric oxygen therapy can induce angiogenesis and regeneration of nerve fibers in traumatic brain injury patients.	Tal S, Hadanny A, Sasson E, Suzin G, Efrati S.	15 patients with PCS	60 sessions (daily)	Improved cerebral blood flow and volume.

Table 2. (Continued)

Study	Authors	Experimental subjects	HBOT details	Outcome
Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post-traumatic stress disorder: a case report.	Harch PG, Fogarty EF, Staab PK, Van Meter K.	25-year-old male military veterans with PCS (case study)	39 sessions (over 26 days) 1.5 ATA for 60 min	Associated with reduction in symptoms of PCS and PTSD
The effectiveness of hyperbaric oxygen therapy as a treatment for postconcussion symptoms.	Hawkins JR, Gonzalez KE, Heumann KJ.	5 level 1 studies	Systematic Review: various HBO_2 Treatments	A literature review showed potential evidence to refute the use of HBOT in PCS treatment rather than support it. This conclusion was drawn from five studies, four of which disproved the use of HBOT and one of which approved HBOT in PCS management.

and visual spatial processing were quantified. In addition to cognitive assessment, brain metabolism and perfusion was evaluated before and after therapy using single photon emission computed tomography (SPECT). The neurocognitive evaluation demonstrated a significant improvement across all areas, with the starkest gains being in the categories of memory and attention. SPECT demonstrated a significant increase in perfusion and metabolism, which in turn correlated to cognitive improvement. One important limitation of this study is that as a retrospective analysis, the researchers were not able to control the exposure, and as such, the HBOT protocol was not the same for all participants. Unique to this study was its implementation of computer generated cognitive test, which may help decrease bias inherent to patient questionnaires.

Example 2: A randomized controlled trial

In this study, 58 PCS patients suffering from concomitant fibromyalgia were randomized to either HBOT or medication arms [71]. Outcomes evaluated included pain intensity assessed by visual analogue scale, and a series of functional symptoms including fatigue and impaired cognition assessed by questionnaire. Compared to medical treatment, HBOT significantly improved both pain and functional deficits. SPECT was also performed to assess metabolic and perfusion differences between HBOT and pharmacologic therapy. Significant activation was found across various Brodmann areas, most notably in the frontal and parietal cortex. This activation was then correlated to beneficial changes reported in patients' questionnaire scores. These findings indicate potentially improved neuroplasticity following HBOT in PCS

patients suffering from concomitant fibromyalgia. This study had several limitations. For one, the results regarding PCS may not be reflective of the general population due to the cohort's concomitant fibromyalgia. Subjects in the sham arm were also treated with fibromyalgia medications which could potentially skew results. The imaging outcomes were correlated to self-reported patient questionnaire scores, however; due to the nature of the study and lack of a true sham arm, the participants were not blinded as to which intervention they received, HBOT or pharmacotherapy.

Example 3: A prospective clinical trial

In this clinical trial, 84 patients who had suffered a prior TBI with severity indexed by Glasgow Coma Scale were evaluated for cognitive function, disability, and functional independence before and after HBOT [72]. The coma recovery scale-revised (CRS-R) was used to measure consciousness, the Stockholm CT score was used to evaluate diffuse axonal injury, and an electroencephalogram was used to evaluate δ to α and δ to θ ratios, as well as relative power. These measures have been determined to be valuable in the assessment of neurological function following TBI [73]. Cognitive impairment was blindly evaluated by three professionals using the Rancho Los Amigos Scale-Revised, Glasgow outcome scale-extended, Functional Independence Measure, and the Disability Rating Scale. Blood biomarkers were also used to evaluate brain injury following TBI and effective recovery following HBOT, including S100β, GFAP, and NSE. HBOT was seen to improve scores from the CRS-R and Stockholm CT, indicating improved consciousness and reduced intracranial hematoma. EEG evaluation demonstrated decreased relative power of the δ band and increased relative power of the α band. This was interpreted as an HBOT-facilitated improvement of the awakened state. Relative to biomarkers, HBOT was found to decrease levels of NSE, S100β, and GFAP, which was interpreted as an improvement in PCS prognosis and an amelioration of cognitive deficits. Limitations of this study include a study protocol where consecutive HBOT was administered for 20 days, rather than a typical course of 5 sessions per week for a total of 8 weeks or 40 sessions. Additionally, many of the patients couldn't participate in proton magnetic resonance spectroscopy and diffusion tensor imaging, which precluded a statistical analysis for clinical curative effects.

Though questions remain regarding its pathophysiology, the observed benefit of HBOT on PCS is now well-documented. Considering the combination of increased clinical awareness of PCS as a pathology and HBOT as a therapeutic option, it is anticipated that additional studies will continue to add to the current knowledge, further revealing important mechanisms.

4.3. Potential risks and contraindications of HBOT for PCS

Though some studies have shown promise for the use of HBOT in PCS management, the literature is not unified on this consensus and HBOT has yet to be approved by

FDA for this use. Additionally, HBOT does not come without its own set of risks and contraindications.

The use of HBOT in the management of PCS is not universally agreed upon. In one study by Cifu *et al.*, patients were subjected to either 40 sessions of HBOT or to a sham arm. Patients were evaluated before and after therapy then evaluated for both between-group differences and within-group differences. There was not a significant difference between the sham group and HBOT group, whereas the within-group differences were somewhat scattered [74]. In a different multicenter, double-blind, and sham-controlled clinical trial by Miller *et al.*, 72 patients were randomized to 40 sessions of HBOT or a sham arm. Regular PCS care was provided throughout for both groups. The Rivermead Post-Concussion Symptoms Questionnaire was then used to assess clinical improvement. There was no significant clinical benefit observed between the HBOT arm and the sham arm as assessed per the questionnaire [75]. Interestingly, the average number of mTBIs sustained per subject was 3, which may make these results less generalizable to the public. Finally, Hart *et al.* conducted a randomized controlled trial with extended in-person follow up assessing PCS symptoms following a large randomized controlled trial that was originally performed for mTBI. Hart's group provided in-person follow up at 24 and 36 months following intervention. This study also found no significant differences between the HBOT arm and the sham arm [76]. These findings demonstrate the current lack of consensus in the literature as to the efficacy of HBOT for PCS and highlight the need for continued studies on this subject.

One of the risks of HBOT is barotrauma, a form of damage to air containing structures within the body due to sudden changes in pressure. The middle ear is especially susceptible to barotrauma during the compression phase of HBOT, the period during which pressures rise. If patients are not adequately instructed on equalizing the middle ear, either by voluntarily contracting the tensor vali palitini muscle to open the eustachian tube, or by self-inflation with the Valsalva maneuver, the body may not be able to compensate for rising pressures and middle ear trauma can ensue [77].

HBOT also has several contraindications that should be ascertained prior to treatment. If patients have any potential obstruction of the eustachian tube due to viral or bacterial illness, polyps, or are otherwise unable to voluntarily equalize the middle ear, they should not participate in HBOT therapy. Another prevalent contraindication is untreated tension pneumothorax, where air enters the pleural space during inhalation but cannot escape during exhalation. The rising external pressures that occur during the compression phase can increase the amount of trapped air within the chest cavity. Any history of cardiovascular disease should also be carefully assessed prior to HBOT. Increased pressures can exacerbate cardiomyopathies, arrhythmias, congestive heart failure, and other cardiovascular

diseases with reduced left ventricular ejection fractions [78]. Individuals with a history of epilepsy should be evaluated for risk of CNS oxygen toxicity which can induce loss of consciousness and tonic-clonic seizure [79]. Finally, patient medications should be carefully screened as some pharmacotherapeutics have side-effect profiles that are exacerbated by HBOT.

4.4. Emerging mechanisms of HBOT

Both human and animal studies suggest that hyperoxia plays a central role in the therapeutic mechanism of HBOT in the context of PCS. By inducing hyperoxia in the brain, HBOT is thought to improve oxygen delivery, mitochondrial function, both neuro and angiogenesis, as well as upregulate anti-apoptotic and anti-inflammatory cytokines. This section provides a brief review of selected mechanisms of HBOT in relation to mTBI. A more comprehensive illustration of HBOT mechanisms has been outlined in the 2021 review by Gottfried, Schottlender, and Ashery [80].

One of the predominant mechanistic explanations is the so called "hyperoxia-hypoxia paradox" or "normobaric oxygen paradox (NOP)," which has been suggested to play a key role in how HBOT confers its effects [81–83]. NOP describes the body's response to a return in normoxic conditions after hyperoxia, as would be experienced during HBOT. Rather than signaling based on absolute oxygen levels, the response to hypoxia seems to be based on relative changes in oxygen. Thus, a return to 21% oxygen from a hyperoxic state may paradoxically upregulate pathways normally induced under conditions of true hypoxia. This includes upregulation of hypoxia-inducible factor 1-alpha (HIF-1α), vascular endothelial growth factor (VEGF), erythropoietin (EPO), sirtuin 1 (SIRT1), and nuclear factor erythroid 2-related factor 2 (NRF2) [80, 81, 84]. HIF-1α promotes cellular survival in hypoxic conditions by signaling cells to rely more on anaerobic metabolism, inducing angiogenesis, and increasing EPO. EPO leads to increased red blood cell production, thus increasing oxygen delivery over time. VEGF increases angiogenesis, thereby promoting better perfusion and delivery of oxygen and nutrients. In addition to effects mediated by VEGF and HIF-1α, HBOT in rodents decreased GABA levels, resulting in preservation of cerebral blood flow [85]. Together, these effects may explain the observed increase in CBF following HBOT treatment and the associated increase in cognitive function [86] (Figure 1).

Elevated NRF2 increases cellular defense against reactive oxygen species and mediates repair and proteolysis of damaged proteins such as microtubules [81, 87, 88]. Microtubule repair is an effect of particular note given the mechanical damage suffered during TBI. NRF2 appears to exert its protective effects in tandem with SIRT1. HBOT preconditioning increased tolerance to cerebral ischemia in animal models, an effect mediated by SIRT1 [89, 90]. Increased SIRT1 expression is associated with concurrent increases in NRF2 activity, as well as antioxidants such as

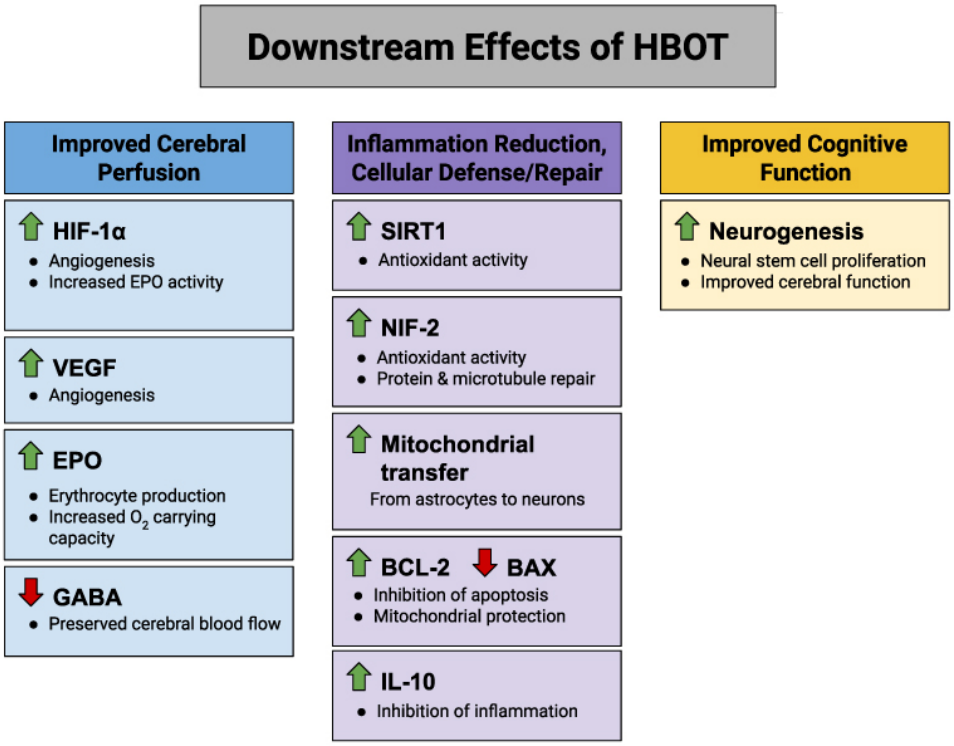

Figure 1. Downstream effects of HBOT.

heme oxygenase 1 and superoxide dismutase 1 [91]. NRF2- and SIRT1-mediated antioxidant activity may thus confer neuroprotection in the setting of post-mTBI cerebral inflammation (Figure 1).

Mitochondria consume roughly 85–90% of inbound oxygen and are the major source of ATP production. Thus, it is likely that HBOT targets mitochondria as part of its mechanism of action [80]. Several animal studies are in accordance with this conclusion. A recent study in rats suggests that HBOT induces transfer of mitochondria from astrocytes to neurons, thus making the neurons more resistant to the neuroinflammation common to mTBI [92]. Finally, another animal study showed that HBOT inhibited mitochondrial-driven apoptosis through increased anti-apoptotic Bcl-2 and decreased pro-apoptotic Bax levels [93]. Though further research should be conducted in humans, these animal studies strongly suggest that HBOT facilitates improved mitochondrial function, thereby mediating a local increase in ATP while promoting protection from apoptosis following injury. Notably, the HIF-1α mediated local shift in metabolism from primarily aerobic to primarily anaerobic may temporarily reduce the burden on mitochondria during periods of synaptic dysfunction due to neurotransmitter and ion imbalances following trauma.

Animal studies suggest that HBOT induces neural stem cell proliferation and angiogenesis [94, 95]. A 2008 study in rats with ischemic brain damage showed that HBOT increased neurogenesis in the subventricular zone and hippocampal dentate gyrus, an area important for spatial navigation [96]. A subsequent study showed HBOT increased spatial memory and learning in rats with TBI, and this was associated with increased hippocampal neuronal activity [97]. VEGF and its associated receptor also appear to be upregulated following HBOT therapy. One study used DTI to demonstrate significantly increased cerebral blood flow and volume as well as improved white and gray matter structures in PCS patients following HBOT therapy, suggesting HBOT plays a role in modulating angiogenesis and neurogenesis [98]. This correlated with clinically improved neurocognitive symptoms. Researchers reported similar findings in pediatric patients suffering from PCS, with HBOT treatment being associated with significantly improved brain MRI microstructural changes and clinical outcome [99]. Taken together, both animal and human studies suggest that HBOT plays a significant role in the upregulation of angiogenic and neurogenic pathways that correlate clinically to improved symptoms [80] (Figure 1).

Perhaps one of the most important proposed mechanisms of HBOT is suppression of neuroinflammation following injury. In a study of post-TBI rats, administration of HBOT significantly increased levels of interleukin 10 (IL-10), an anti-inflammatory cytokine, as well as inducing both neuro and angiogenesis [100]. These anti-inflammatory effects are also seen in rats with Alzheimer's disease that are treated with HBOT. In conjuction with the previously mentioned antioxidant and reparatory effects of NRF2 and SIRT1, HBOT may play a role in modulating neuroinflammation across a spectrum of neurocognitive disorders [101].

4.5. Neuroimaging and novel biomarkers

As neuroimaging continues to advance, novel biomarkers are being identified and the current understanding behind mechanisms of PCS is growing. Although many of these identifiers have not yet entered the clinical arena, continued efforts in basic and translational research will pave the way to a more nuanced and personalized diagnostic approach and treatment plan for future clinicians. Below, several studies are outlined investigating biomarkers thought to be involved in HBOT for PCS.

A prominent biomarker in HBOT for PCS is brain tissue partial oxygen pressure. A technique used to capture this marker is blood oxygenation level dependent (BOLD) imaging. BOLD is an MRI technique used to determine regional variations in cerebral oxygen use following a stimulus. BOLD imaging is based on the different magnetic properties of oxygenated and deoxygenated blood. When neurons are stimulated, their metabolic rate increases, resulting in a concomitant increase in the demand for oxygen. In return, CBF increases to that area, likely through astrocyte

signaling and functional hyperemia as previously discussed [35]. Though CBF is temporarily increased, local tissues may not metabolize oxygen in a proportional manner. In turn, the brain tissue partial oxygen pressure rises, and this rise changes the local magnetic signature of the blood. In this manner, BOLD imaging can detect both initial rises in oxygenation as well as this lingering change, also known as post-stimulus undershoot. Post-stimulus undershoot of the BOLD signal combined with HBOT may shed further light on chronic mitochondrial dysfunction and inefficiencies.

Though seen as early as 1963, SPECT is an imaging technique that has benefited from several recent developments and is now more optimized for characterizing PCS and the therapeutic effect of HBOT [102, 103]. Similar to BOLD, SPECT is used to detect changes in CBF and tissue metabolism. However, unlike BOLD, SPECT relies on CT and an injectable radioactive tracer that emits gamma rays, which are in turn captured by a gamma camera. When compared to standard MRI and CT, SPECT has demonstrated a significantly higher negative predictive value for TBI, reaching close to 100% [104]. Another area in which SPECT excels compared to BOLD is the detection and monitoring of neurotransmitters. Relevantly, SPECT studies have been considered for their potential to monitor glutamate, serotonin, and other neurotransmitters as well as their respective receptor density [105–107]. Since glutamate is considered the main regulator of functional hyperemia, SPECT could be used to monitor astrocyte signalling via glutamate, and glutamate receptor regulation under HBOT, thereby informing the current body of knowledge of neurovascular coupling in different states of oxygenation [35, 105].

Diffusion weighted imaging (DWI), also known as diffusion tensor imaging (DTI), is an MRI technique that relies on the Brownian movement of water molecules in the brain. DTI compares isotropic diffusion to anisotropic diffusion, providing a quantitative evaluation of diffusion and visualization of white matter tract direction [108, 109]. White matter axons usually confer a great deal of anisotropy in a healthy brain. Injured white matter will present as decreased functional anisotropy (FA) on DTI. Immediately following injury, DTI reveals increased FA and decreased mean diffusion (MD), possibly due to axonal edema. In the post-acute and chronic phases of recovery, FA decreases and MD increases [110, 111].

One recent study correlated poor performance on the Montreal Cognitive Assessment (MoCA) in patients with persistent concussion symptoms with regional abnormalities on DTI [112]. Several other studies have shown the corpus callosum to be particularly affected following TBI [113, 114], though different studies have implicated other brain regions. In the context of PCS characterization, DTI has promise to identify key biomarkers, but it is not without limitations. In particular, DTI assumes Gaussian movement of water molecules. In practice; however, cerebral

water diffusion often does not follow such Gaussian movement, and DTI imaging will not account for that. Diffusion kurtosis imaging (DKI) accounts for this non-Gaussian diffusion and thereby paints a more accurate picture of white matter axon tracts. This may permit higher-grade characterization of PCS [115–117]. Neurite orientation dispersion and density imaging (NODDI) is another diffusion-based MRI technique that may have increased sensitivity over DTI studies for detecting white matter injury. A 2022 study of NODDI, DKI, and DTI in patients with mild TBI by Huang *et al.* showed significant correlation between white matter changes and cognitive deficit, especially in the corpus callosum [118]. Continued research using advanced, diffusion-based neuroimaging techniques such as DTI, DKI, and NODDI have the potential to improve the current understanding of PCS and its underlying pathophysiology. Doing so may enable identification of predictive biomarkers and inform the clinical use of therapies like HBOT.

5. Clinical implications, data sharing, and machine learning

5.1. Clinical implications

Essential to a discussion of HBOT in the management of PCS are clinical considerations such as cost, accessibility, patient selection criteria, and integration with existing PCS protocols.

Since HBOT is considered off-label for managing PCS, it is yet to be covered by most insurance plans. Out-of-pocket costs without coverage can accumulate quickly, with some private centers charging between $250–$600 per session. Since HBOT is often conducted in a series of 40–60 consecutive sessions, cumulative costs can amount to over $36,000. This alone may outweigh the benefits of HBOT for many patients, thereby also precluding the accumulation of a larger series of cases for further study.

Perhaps the greatest barrier to effectively using HBOT for PCS is accessibility. Hyperbaric oxygen chambers are not typically found in outpatient neurology settings. Many regions lack the required equipment altogether. Patients in these settings are required to travel long distances to a tertiary care center where chambers are used for wound healing, decompression sickness, and other FDA-approved indications, or to a private hyperbaric clinic that may have higher costs with less oversight.

Patient selection criteria is another important consideration, as not all patients will benefit equally from HBOT. Headache and cognition, in particular, have been associated with improved outcomes following HBOT. For other symptoms of PCS like insomnia, vertigo, and vision anomalies, the benefits are less clear. Clinicians

must consider the entire clinical context, including not only the duration and nature of PCS symptoms, but also any potential contraindications, prior to the decision to treat with HBOT.

5.2. Data sharing and machine learning

A common thread in studies regarding the use of HBOT for PCS is the potential benefit of improved data sharing. Though interest in HBOT for PCS and mTBI is increasing, many studies are currently limited by small sample sizes, non-universal endpoints, and disparate diagnostic criteria. Additionally, the majority of studies on HBOT and PCS are conducted in separate contexts, resulting in the collection of potentially synergistic but disconnected data. More cross-center collaboration is needed to better elucidate the effects of HBOT on PCS and to prioritize future directions in the field. With the role of machine learning growing in medicine, data-sharing agreements can help create robust imaging and symptom data banks for analysis and categorization. The studies below highlight the potential of machine learning in the context of improved data-sharing policies.

Example 1: ODC-TBI

The Open Data Commons for TBI (ODC-TBI) pools individual subject data into a central location, allowing for high-sample, feature-rich data sets that are ideal for training machine learning software. Furthermore, ODC-TBI works to implement FAIR (Findability, Accessibility, Interoperability, and Reuse) principles, a guideline set forth to improve machine ability to find and access data with minimal human intervention [119]. Chou *et al.* demonstrated the utility of ODC-TBI in the context of machine learning by analyzing multi-cohort data [120]. Their analysis resulted in machine recognition of TBI-associated inflammatory markers including IL-1β, TNF-α, iNOS, Ym1, CD206, and TGF-β. Machine learning and pattern recognition promise to take these approaches to a more advanced level, facilitating normalized classification and prediction of disease based upon current standards and novel biomarkers, while simultaneously reducing human-bias.

Example 2: Evaluating EEG biomarkers following HBOT

This 2019 study by Lewine *et al.* sought to use machine learning in a way that increases the validity of current biomarkers used to evaluate PCS following HBOT [121]. In specific, the authors evaluated EEG markers of mTBI, including absolute and relative power across δ, θ, α, β, and γ waves, as well as functional connectivity. Following analysis, machine learning methods were employed to augment their multivariate analysis, leading to an improved model with 75% predictive accuracy in the recognition of patients with mTBI symptoms compared to the control.

Example 3: Machine recognition in DTI imaging

This 2023 study demonstrated machine recognition of biomarkers via DTI imaging [122]. First, DTI and functional MRI (fMRI) were used to characterize white matter deficits and abnormalities in cerebral connectivity in patients with mTBI. DTI revealed significant white matter lesions in the perithalamic region, indicating injury to the thalamic reticular nucleus. fMRI analysis also showed resting state hyperconnectivity among thalamic subdivisions, implying a failure to properly integrate and relay information within the thalamus. In patients diagnosed with PCS, thalamocortical coherence was found to be significantly elevated, suggesting a potentially powerful biomarker. They then used baseline imaging and demographic data to train a machine learning based long-term predictive model of post-concussion syndrome. This model was highly predictive of PCS development and successfully predicted symptoms in rodents.

Further calibration and refinement of machine learning will continue to clarify the link between HBOT and PCS symptom amelioration. Some of the most exciting applications of machine learning involve its potential to find and synthesize isolated but related data for discovery in new contexts. Since HBOT and PCS are frequently studied apart, machine learning may hold the key to discovering unforeseen links. Regardless of what the future may hold, these tools are already serving to build upon the current foundation of knowledge regarding PCS and HBOT, in turn yielding pragmatic results for patients and clinicians alike.

6. Future directions

Despite the growing body of research regarding the mechanisms of HBOT as a treatment for PCS, there is yet to be a complete consensus as to its efficacy and potential. Many of the studies that have shed light on the current understanding of HBOT have been conducted with patient samples that may not adequately represent the general public. The studies that report no significant differences, in specific, tend to have patient pools consisting exclusively of military personnel with a potentially higher average lifetime number of mTBIs. Future studies may benefit from a more heterogenous sample of patients, and large cohort multi-center studies would be beneficial. Another consideration for future trials is the inclusion of more neuroimaging such as BOLD, SPECT, and DWI, to objectively follow subject progression throughout the therapy. Some of the current studies rely solely on patient questionnaires for primary outcome measures, and this may not adequately reflect the full effect of HBOT. Finally, future study designs may also explore the use of artificial intelligence to detect relevant PCS biomarkers, which could further elucidate the long-term effects of HBOT on neurogenesis and synaptic function.

7. Conclusions

Though questions remain regarding the proposed pathophysiology of PCS, HBOT has been observed to be an effective therapeutic option. The prevailing mechanism is a proposed mitochondrial dysfunction following mTBI, as evidenced by decreased oxygen extraction fraction and additional imaging biomarkers. HBOT likely ameliorates these effects by increasing cerebral perfusion and oxygenation while simultaneously decreasing residual inflammation. Data-sharing, machine learning, and advanced imaging techniques hold much promise toward increasing the current body of knowledge regarding the outcomes of HBOT in the management of PCS. As these outcomes are further elucidated, HBOT may become an integral component of PCS treatment.

Conflict of Interest

The authors declare no conflict of interest.

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