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Hyperbaric Oxygen Therapy versus placebo for post-concussion syndrome (HOT-POCS): A randomized, double-blinded controlled pilot study

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ABSTRACT

Post-Concussion Syndrome (PCS) refers to the persistence of physical, cognitive, and emotional symptoms following mild traumatic brain injury (mTBI)/concussion, occurring in roughly 15–30% of individuals. Hyperbaric oxygen therapy (HBOT) has been suggested as a potential treatment for PCS; however, the evidence to date is mixed due to inconsistencies in the treatment protocol and focus on veterans with combat-related injuries, which may not be generalizable to the general population. The goal of Hyperbaric Oxygen Therapy for Post-Concussion Syndrome (HOT-POCS) is to assess the efficacy and safety of HBOT for the treatment of PCS in the civilian population. This randomized, controlled pilot study will be using a standardized HBOT protocol (20 sessions of 100% O_2 at 2.0 atm absolute [ATA]) compared with a true placebo gas system that mimics the oxygen composition at room air (20 sessions of 10.5% O_2 and 89.5% nitrogen at 2.0 ATA) in a cohort of 100 adults with persistent post-concussive symptoms 3–12 months following injury. Change in symptoms on the Rivermead Post-concussion Questionnaire (RPQ) will be the primary outcome of interest. Secondary outcomes include the rate of adverse events, change in the quality of life, and change in cognitive function. Exploratory outcome measures will include changes in physical function and changes in cerebral brain perfusion and oxygen metabolism on MRI brain imaging. Overall, the HOT-POCS study will compare the efficacy of a standardized HBOT treatment protocol against a true placebo gas for the treatment of PCS within 12 months after injury.

1. Introduction

1.1. Background/statement of the problem

Mild traumatic brain injury (TBI)/concussion can lead to a variety of physical, emotional, and cognitive symptoms, including headaches, sensitivity to light/noise, balance problems, vertigo, nausea, vomiting, anxiety, sadness, irritability, sleep disturbances, fatigue, confusion, memory, and concentration problems. Most people are "back to normal" within three weeks of injury; however, approximately 15–30% of individuals develop persistent symptoms, known as post-concussion syndrome (PCS) [1,2].

Clear guidelines for treatment of individuals with persistent symptoms following concussion are lacking. Altered neurotransmission, inflammation, increased oxygen demand, and decreased cerebral blood flow may contribute to PCS pathophysiology [3], all of which may benefit from hyperbaric oxygen treatment (HBOT) [4–7]. During HBOT, the patient breathes 100% oxygen intermittently while the whole body is pressurized within a hyperbaric chamber, resulting in intermittent hyper-oxygenation that can promote the healing in tissues with inflammation, high oxygen requirements, and decreased blood flow [8–10]. HBOT induces a controlled production of reactive oxygen and nitrogen species in the tissues, causing activation of various cellular processes and pathways, such as increased growth factor (e.g., hypoxia-inducible factor 1-α, vascular endothelial growth factor, and stromal-derived factor 1) production, mobilization of bone

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marrow–derived stem/progenitor cells (CD34), and the reduction of neutrophil adhesion (modification of integrin β-2) [11,12].

The use of HBOT for PCS is considered experimental and controversial. Animal models have shown neuroprotective effects of HBOT when administered acutely after injury; [13] however, evidence in human trials has been inconsistent [14–19]. Variability in patient populations, HBOT treatment interventions, and sham/placebo comparison groups are potential reasons for the inconsistency of research findings. Most studies utilize individuals with military populations [15–18, 20–23], many of whom had a distinct mechanism of injury (i.e. blast injury) that is uncommon in the civilian population. Additionally, military populations may have additional factors relating to exposure to trauma and repeated concussive or sub concussive exposures. HBOT treatments have ranged from 100% FiO_2 as low as 1.5 atm absolute (ATA) [14,18,20] to as high as 2.4 ATA [23], limiting the ability to compare consistent treatment protocols. Furthermore, the sham intervention may provide therapeutic benefit. Most interventions utilized room air at 1.2–1.3 ATA as the sham treatment; [20,21,23,24] therefore, participants in the control groups were receiving air at an increased ambient pressure (resulting in an increased partial pressure of inspired oxygen and inspired nitrogen). Well-designed studies accounting for the limitations of the prior research are necessary to evaluate the efficacy of HBOT for PCS.

The proposed study will expand upon the existing research in the following ways in multiple ways. First, we will enroll individuals from the general population within the first 3–12 months post-injury to assess the efficacy of HBOT during the subacute rather than chronic period after concussion. Second, we will be using the Undersea and Hyperbaric Medical Society (UHMS) approved treatment protocol – 2.0 ATA for 90 min. Third, we will utilize a novel placebo gas system that will ensure that the control subjects will receive the equivalent of 0.21 ATA of O_2 to mimic room air. Lastly, we will examine changes in functional magnetic resonance imaging for objective evidence across treatment and control groups. The proposed study will be a randomized, double-blinded, exploratory trial examining the efficacy and safety of Hyperbaric Oxygen Therapy for individuals with post-concussion syndrome.

1.2. Objectives and aims

Objective 1: To evaluate the efficacy of 20 sessions of 90 min HBOT (100% O_2 at 2.0 ATA) compared with sham treatment to improve outcomes for adults with persistent PCS 3–12 months after mild TBI/concussion.

Aim 1.1 (primary aim): To determine if HBOT decreases symptom burden in persons with persistent PCS 3–12 months after mild TBI/concussion. *Hypothesis*: Individuals receiving HBOT will have decreased PCS symptoms after 20 sessions as measured by the Rivermead Post-concussion Questionnaire (RPQ) compared with those receiving sham treatment.

Aim 1.2 (exploratory aim): To determine if HBOT improves cognitive function in individuals with persistent PCS 3–12 months after mild TBI/concussion. *Hypothesis*: Individuals receiving HBOT will have improved cognitive function based on NIH Toolbox Cognition Battery compared with those receiving sham treatment.

Aim 1.3 (secondary aim): To determine if HBOT improves quality of life in persons with persistent PCS. *Hypothesis:* Individuals receiving HBOT will report better quality of life based on the short form survey 36 (SF-36) compared with those receiving sham treatment.

Objective 2 (secondary objective): To assess the safety and tolerability of hyperbaric oxygen treatments and compliance with treatment in adults with persisting post-concussion syndrome. *Hypothesis:* There will be no difference in adverse events based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [25] between those receiving HBOT and sham treatment.

Objective 3 (exploratory objective): To evaluate changes in brain perfusion and cerebral metabolic rate for oxygen utilization ($CMRO_2$) before and after 20 treatments and evaluate the association of these findings with symptom resolution.

2. Methods

2.1. Study design

A summary of the study procedures is shown in Fig. 1. This study is a randomized, double-blind, SPIRIT compliant, controlled pilot study. Participants, investigators, outcome assessors, and data analysts will all be blinded to treatment allocation. HBOT technicians will receive the assignment directly from the RedCap randomization. This study has been approved by the UT Southwestern Medical Center and Texas Health Presbyterian Institutional Review Boards (IRB) and has been registered at ClinicalTrials.gov (#NCT05643482).

2.2. Study setting

The sessions of HBOT and sham therapies will be administered in the Perry Baromedical Corp. Sigma multiplace hyperbaric chamber at the Institute for Exercise and Environmental Medicine (IEEM) located at Texas Health Presbyterian Hospital Dallas. The IEEM's Hyperbaric Medicine Program has Level 1 (with Distinction) Accreditation through the Undersea and Hyperbaric Medical Society. Baseline and outcome cognitive and self-report assessments will take place in the same building. All imaging will occur at the Advanced Imaging Research Center at UT Southwestern Medical Center using the same magnet.

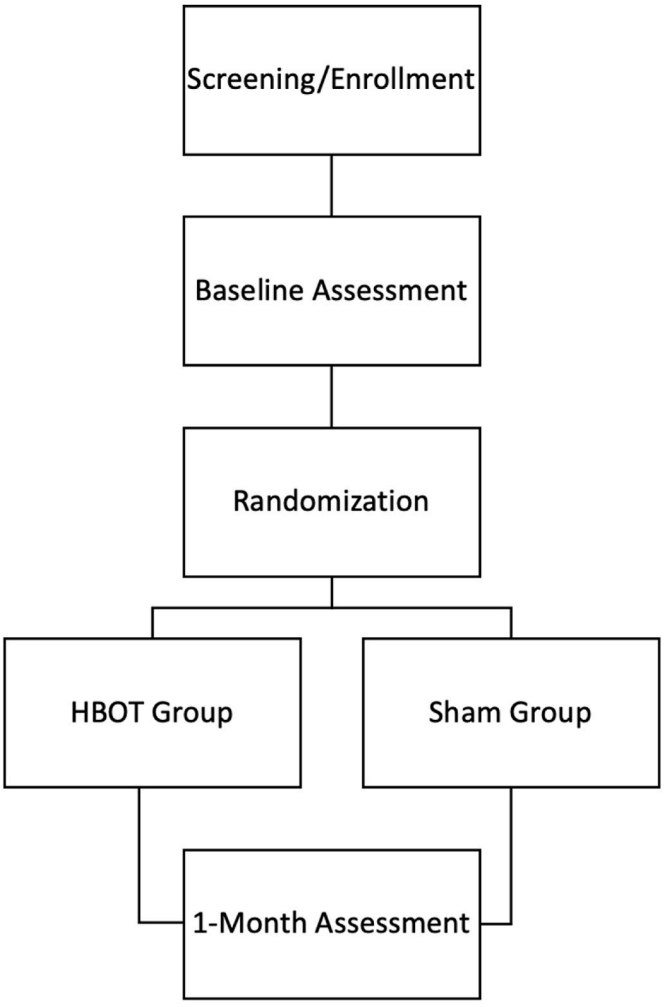

Fig. 1. Study flowchart.

2.3. Participants/recruitment

One hundred individuals with persistent post-concussion symptoms 3–12 months post-injury will be recruited for this study. The threshold of persistent symptoms for treatment will be determined by at least 3 moderate to severe (score 3–4) symptoms or a total score of at least 10 with at least 1 symptom rated moderate to severe on the Rivermead Post Concussion Questionnaire (RPQ) [26]. Other inclusion/exclusion criteria are shown in Table 1. Participants will be primarily recruited from outpatient clinics at UT-Southwestern Medical Center and Parkland Health and Hospital System as well as the North Texas Veterans Affairs Medical Center. Any patient recruited from the VA facility will be those with stateside injuries not sustained in combat theater. Clinic providers will be educated about the study and flyers will be placed in the clinics; research staff will screen clinic rosters for potential candidates. We will also be recruiting from the North Texas Concussion Registry (ConTex) which is a longitudinal registry for concussion located at UT-Southwestern. Individuals aged 18 to 65-years-old who have a diagnosis of concussion entered in the electronic medical record within the past 12 months will be sent MyChart messages regarding the study through the Epic medical record system.

All individuals will complete an initial screening checklist with the research coordinator either in person or by telephone (Supplementary Table 1) to assess medical eligibility for the study. Individuals that meet inclusion and exclusion criteria will be scheduled for a 10–15-min virtual visit with one of the study physiatrists for review of their medical history and current symptoms (Supplementary Table 2) in regards to their concussion prior to scheduling an in person visit at the hyperbaric medicine facility, where they will complete written informed consent and undergo a medical evaluation by one of the hyperbaric medicine physicians to determine their appropriateness for HBOT treatment. Written informed consent will be obtained from research study coordinators, and any protected health information obtained will only be used for this study.

Demographic information collected from the participants will include age, sex, race and ethnicity, years of education, current employment, and past medical history. History of prior TBI will be collected using the Ohio State University (OSU) TBI Identification Method [27]. Injury-related information will include mechanism of injury, date of injury, time since injury, duration of LOC, Glasgow Coma Scale (GCS), length of PTA, results from the head CT (if completed), and associated injuries. Participants will be queried for information about any current or prior medications or therapy. All data will be collected and stored in RedCap and Florence eBinder. Reliability and validity for all measures collected are presented in the protocol.

To ensure patient retention in the study, the participants will be scheduled for treatments by the hyperbaric staff on schedules that are convenient for the participants and treatments will be planned for the same time every day to decrease risk of confusion. Participants will also be paid upon completion of the study. Weekly assessments of change in symptoms will be completed to minimize data loss for those that chose to drop out of the study.

2.4. Intervention – hyperbaric or sham sessions

Each group will undergo 20 sessions of HBOT or sham therapy at 2.0 ATA for 90 min in a multiplace chamber, one session per day, over 4–5 weeks. The hyperbaric oxygen treatment group (group A) will breathe 100% oxygen. The sham group (group B) will breathe 10.5% oxygen and 89.5% nitrogen, which mimics the partial pressure of oxygen breathed in regular air at sea level pressure. Research participants will be provided an orientation presentation and tour of the hyperbaric facility, to include protocols and safety features. The staff at the IEEM's Hyperbaric Medicine Center are all certified hyperbaric registered nurses or technicians. A trained emergency response team is readily available per hospital policies and procedures in the case of an adverse event. No

Table 1
Summary of Eligibility Criteria and Rationale. An asterix (*) indicates relative exclusion criteria. Individuals with any of these listed items identified during initial screening or examination will be enrolled only if the hyperbaric medicine physician believes that they will be medically appropriate to complete HBOT.

Inclusion Criteria	Rationale
Age 18 to 65-years-old	This study is focused on adults with concussion. Limiting upper age ranges will reduce the likelihood of impacts on cerebrovascular blood flow outside our intervention.
Evaluated within 48 h of injury and given a diagnosis of concussion/mild TBI by a medical professional	To ensure appropriate diagnosis.
Onset of injury 3–12 months prior to screening visit	Many individuals with concussion will have resolution of symptoms within 3 months due to natural recovery. Individuals more than 12 months following injury may be less responsive to treatment due to the chronicity of their symptoms.
Have at least 3 symptoms that are moderate to severe (score 3–4) OR a total score of 10 or more with at least 1 symptom rated moderate to severe (3–4) on the Rivermead Post-Concussion Questionnaire (RPQ).	Only individuals with persistent symptoms will be enrolled in the study. The cut off of 3 moderate to severe symptoms or total RPQ score of 10 or more with at least one moderate to severe symptom was chosen to improve sensitivity to see responsiveness to treatment.
Exclusion Criteria	**Rationale**
Glasgow Coma Scale (GCS) score <13	Mild TBI is defined as GCS 13–15; therefore, GCS less than 13 would be considered a more severe injury
Required surgical intervention for TBI	Individuals who required surgical intervention for management of their TBI would have suffered more severe injury than simply mild TBI/concussion
Currently undergoing physical, occupational, or speech therapy	To control for the type of interventions people are receiving for PCS outside of the study, individuals currently undergoing therapy will be excluded. They may be rescreened for participation after completing therapy.
Planned medication change in the next 3 months	Individuals will need to be stable on their current medication regimen throughout the study to decrease the influence of treatments outside the intervention on changes in symptoms.
Active neurologic disease (other than concussion) or psychotic illness	To focus on the influence of PCS on the current symptoms and outcome measures
Pneumothorax or history of spontaneous pneumothorax	Untreated pneumothorax may become a tension pneumothorax during decompression when gas expands faster than it can escape, causing respiratory distress, cardiovascular collapse, and cardiac arrest. Individuals with history of pneumothorax are at higher risk for pulmonary barotrauma.
Pregnancy or trying to get pregnant	The effects of HBOT on the developing fetus are unknown.
Seizures*	Hyperbaric oxygen treatment may increase risk of seizures. Individuals with a seizure within the 3 months or on current medications for treatment of seizures will be excluded. Any persons with history of seizures greater than 3 months ago and not on medications will be reviewed by the hyperbaric medicine physician before inclusion.
Fever	High fever can decrease the seizure threshold, making oxygen toxicity more likely. Individuals with high fever (>39° Celsius or >102.2 Fahrenheit) will be referred to their primary care physician

(*continued on next page*)

Table 1 (*continued*)

	for work-up and management prior to enrolling in the study. Individuals will only be able to undergo HBOT if they are afebrile at time of each HBOT treatment.
Inability to equilibrate the ears	Individuals will be taught maneuvers to help equilibrate the ears to decrease risk of barotrauma. Those unable to equilibrate their ears despite these maneuvers and decongestants will not be enrolled.
Pulmonary fibrosis	Increased risk of pulmonary barotrauma with air embolism and/or pneumothorax during HBOT due to trapped gas leading to barotrauma. Air trapping is common in patients with interstitial lung diseases.
Asthma, chronic obstructive pulmonary disease (COPD) or other breathing-related disorder*	Asthma and chronic obstructive pulmonary disease (COPD) can result in air trapping and the development of pulmonary barotrauma. Asymptomatic pulmonary blebs and bullae found on plain chest radiographs also serve as a contraindication due to the potential air trapping progressing to a pneumothorax.
Hypertension*	Absolute rises in blood pressure do occur as a result of HBOT due to peripheral vasoconstriction. Those with hypertension will be referred to their physician for management prior to enrolling in the study.
Heart failure or pulmonary edema	Heart failure is a relative contraindication to HBOT based on severity and current treatment, due to the risk of exacerbation of congestive heart failure with pulmonary edema. The underlying mechanism is not entirely clear, but one possible mechanism is ventricular imbalance. With hyperbaric oxygen therapy, peripheral vasoconstriction causes increased left ventricular afterload. This same hyperoxia results in pulmonary vasodilation that reduces right ventricular afterload. In the setting of left heart failure, the left ventricle is afterload dependent. Therefore, any increase in afterload may result in a worsening of left-sided cardiac output. A decrease in left cardiac output relative to right can result in additional fluid volume in the pulmonary vascular bed. Risk of HBOT outweighs benefit of this study.
Implanted electronic device, or device with batteries (such as pacemaker, defibrillator, vagus nerve stimulator, etc.)	Devices can malfunction or deform under pressure. Before approving the study subject, we have to make sure that the manufacturer has tested and certified the device at a pressure greater than 2 ATA.
Congenital spherocytosis	In this condition, the red cells are quite fragile and increased O2 levels have been shown on occasion to produce hemolysis.
Optic neuritis	History of optic neuritis or sudden blindness has traditionally been a relative contraindication to undergoing HBOT. There have been anecdotal reports of acute blindness associated with HBOT in some patients with a history of optic neuritis. Although there have been limited studies on these patients.
Otosclerosis surgery	In these participants, failure to equalize pressure in the middle ears might cause bending or displacement of the strut, with severe degradation of hearing.
Retinal or vitreous surgery within the last 3 months	Eye surgeries could be problematic if there is any air or gas trapped in the eye, as expansion/contraction of gas could damage the eye.
Prior thoracic surgery	A history of thoracic surgery may increase the risk of atelectasis and pneumothorax. A thorough evaluation (including chest CT scan) should be performed before treating patients with HBOT and these evaluations are not covered in this research study.
Claustrophobia	Individuals with claustrophobia would not be able to tolerate the HBOT treatments as they will be expected to be in an enclosed chamber for at least 90 min for each session
Upper respiratory infection/chronic sinusitis*	Increased risk of barotrauma to the middle ear and paranasal sinuses.
Active infection	To prevent cross infection of other persons in the enclosed chamber. Individuals can be rescreened once they are cleared from the infection.
Drug or Alcohol Abuse*	Individuals will be excluded if they report use of illicit drugs or scoring positive on the CAGE-AID.
Use of glucocorticoids within one month prior to screening visit,	Glucocorticoids may increase the risk of oxygen toxicity
Current nitrate medication use	The vasoconstriction effects of HBOT interferes with the vasodilatory effects of nitrates
Bleomycin use	Can cause pulmonary fibrosis and increase risk of pneumothorax.
Current opioid analgesics	Will enhance the risk of oxygen toxicity via CO2 retention, leading to central vasodilation. Depress respiration by reducing the reactivity of the medulla to CO2 leading to a rise in arterial PCO2 causing the blood vessels of the brain to dilate. Due to the increased blood flow, the amount of dissolved oxygen rises in the brain tissue. This rise speeds the development of CNS oxygen toxicity (convulsions). Additionally, opioid use may significantly exacerbate perceived heat, resulting in an uncomfortable treatment experience.

compensation will be provided in the case of an adverse event as outlined in the consent form.

Prior to each hyperbaric session, a hyperbaric physician, who is fellowship trained and Board Certified in Undersea and Hyperbaric Medicine, will review any medical updates and discuss any findings and concerns with research participants. Each participant will also be evaluated immediately before and after each session to assess potential contraindications and adverse outcomes. If the participant has a temperature of 99.8 °F or greater when vital signs are checked prior to the treatment, the participant will need to be evaluated by the hyperbaric oxygen treatment physician to determine whether they can proceed with the study treatment. The hyperbaric physician will directly supervise each hyperbaric session, will be present in the HBOT unit during the sessions, and will be immediately available to furnish assistance and direction.

Participants will have a baseline otoscopy evaluation performed by the hyperbaric physician and be instructed in proper techniques to equalize inner ear pressure prior to the first hyperbaric exposure. If participants have difficulty equalizing the pressure in their ears, the pressurization of the chamber will be stopped, and the pressure reduced until equalization is achieved. At this point, the hyperbaric physician might order the use of an over-the-counter decongestant nasal spray containing oxymetazoline, such as Afrin. Subsequently, the pressurization of the chamber may continue, albeit at a slower rate of pressurization. This process minimizes the likelihood of barotrauma. If the participants continue to have difficulty equalizing the pressure in their ears despite the above measures, treatment will be aborted before barotrauma occurs. Re-evaluation by otoscopy will be performed after

exiting the hyperbaric chamber by the hyperbaric physician. No participants will be purposefully allowed to progress to the point of barotrauma.

Initial compression from sea level (1 ATA) to 2.0 ATA will occur over 20 min during the first hyperbaric session and will be based on participant tolerance thereafter (ear discomfort). Subsequently, participants will be maintained at 2.0 ATA (study subjects breathing 100% O2 and control subjects 10.5% O2) for 90 min. By using a consistent pressure of 2.0 ATA for both the HBOT and sham groups, both groups of participants can be treated during the same session within the multiplace chamber. This allows for true blinding of all study staff, including the treating hyperbaric medicine physician and nurses that interact with the participants. The only staff member that will know the treatment group will be the hyperbaric technician that only interacts with the participant prior to randomization. Two 5-min "air breaks" (at 30 and 60 min) will be added to the study group. "Air breaks" are used to prevent oxygen toxicity. These will be instituted for participants in the study group only (not required for the control group) and additional prophylactic "air breaks" will be given to participants experiencing early symptoms of CNS toxicity (nausea, hiccoughs, twitching of the periorbital or facial muscles, tinnitus/vertigo, gustatory or olfactory hallucinations and/or fluctuations in heart rate). During these two 5-min "air breaks" for the study group, the control group will remain breathing 10.5% O2. The 90-min time will begin when participants reach the target chamber pressure of 2.0 ATA and begin breathing through the hood treatment system. Subsequently, the hoods will be removed and the depressurization of the hyperbaric chamber to the surface (sea level pressure) will begin. During decompression, participants will be instructed to avoid holding their breath, glottis closure, or other maneuvers that may increase the risk of pulmonary barotrauma. Decompression will be at a maximum rate of 10 feet of seawater per minute (no faster than 3 min). In the event of an emergency, or if participants request to stop treatment, the chamber will be brought to sea level pressure (surface) and the participant will be treated accordingly.

2.5. Outcome measures

Outcome measures and timing of collection are shown in Tables 2 and 3. Measures will be administered at baseline prior to randomization and again within a week of completion of treatment and at 3 months. The examiner will remain blinded to assignment. A subset of 25 individuals in each group will be randomized to undergo MRI with arterial spin labeling (ASL) to evaluate for changes in cerebral blood flow and $CMRO_2$ before and after HBOT treatment (exploratory aim 3). To minimize the acute effects of HBOT on cerebrovascular blood flow and CMRO2, individuals will be tested 7 days after last HBOT treatment. Additionally, all participants will be asked to guess their assigned group (HBOT or sham) to assess the strength of the blinding during the study.

2.6. Sample size and allocation to groups

Sample size has been estimated using the available evidence on the primary outcome RPQ-3 from existing research on a trial of 20 sessions of HBOT at 2.0 ATA.5 The observed changed mean scores (standard deviation) of RPQ-3 from baseline after 13 weeks of intervention were 1.2 (2.2) and −0.3 (2.7) in Sham and HBOT groups respectively, which converted into an effect size of 0.60. Using a two-sided independent *t*-test at a 5% level of significance with 80% of minimum study power, we estimate needing 43 subjects in each group to detect this expected effect size (or group difference). Accordingly, a total of 100 participants (50 per group) will be randomized to allow for an approximately 15% loss to follow-up.

Participants will be randomized between HBOT treatment and control group with a 1:1 allocation ratio and stratified by sex via computer generated using permuted block of random sizes. Additionally, 25 participants receiving HBOT and 25 controls will be randomly selected from

Table 2
Outcome Measures. Outcome measures will be assessed prior to randomization (baseline), after completion of 20 treatments, and 1-month following last treatment. The Global Impression of Change and Percent Back to Normal will also be assessed weekly/after every five treatments. See Table 3 for detail of timing of outcomes.

Outcome	How Assessed
Symptom Burden[a]	The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is a 16-item questionnaire of cognitive, behavioral, and physical symptoms experienced following a mTBI. The RPQ is rated on a 0–4 scale with scores ranging from 0 to 64. Higher scores indicate more severe symptoms [26]. The RPQ-3 is the total score of the first three items of the RPQ and includes "headaches," "feelings of dizziness," and "nausea and/or vomiting". The RPQ-13 is the total score for the following 13 items in the scale [26].
Quality of Life[b]	The 36-Item Short Form Survey (SF-36) consists of 36 items and measures quality of life via eight different domains including vitality, physical functioning, social functioning, emotional role, physical role, general health, social functioning, and mental health [33].
Cognition[c]	The NIH Toolbox Cognition Battery (NIHTB-CB) consists of five subtests measuring fluid cognition. Picture Sequence measures (episodic memory), List Sorting (working memory), Pattern Comparison (processing speed), Flanker Inhibitory Control and Attention Test (attention), and the Dimensional Change Card Sort task (executive function) [34]. The Trail Making Test is a measure of executive function and processing speed and consists of Trails A and Trails B [35, 36].
Physical Function[c]	The NIH toolbox motor battery measures strength (Grip Strength Test), dexterity (9-Hole Pegboard Test), balance (Standing Balance Test), endurance (2-Minute Walk), and locomotion (Meter Gait Speed Test) [37].
Psychological/Mood Symptoms[c]	The Brief Symptom Inventory (BSI) contains 18 items with 3 subscales measuring Depression, Anxiety, and Somatization. The total raw score represents the Global Severity Index (GSI). Scores on each of the 3 subscales range from 0 to 24 and total GSI scores range from 0 to 72. Higher scores on the subscales and total GSI are indicative of more severe psychological/mood symptoms [38].
Impression of Change[b]	The Global Impression of Change scale is a seven point scale in which participants are asked to rate how much the treatment has changed their activity limitations, symptoms, emotions, and overall quality of life [39].
Percent Back to Normal[b]	Participants will be asked to rate what percent they feel back to their pre-injury self.
Cerebral Blood Flow and Cerebral Metabolic Rate for Oxygen Utilization ($CMRO_2$) [3]	A subset of 25 individuals from each group will be randomized to undergo additional MRI with arterial spin labeling (ASL) imaging before and after the HBOT treatments. ASL will assess the cerebral blood flow noninvasively by magnetically labeling inflowing blood. Global venous oxygenation will be measured using the TRUST MRI scan to assess the $CMRO_2$.

[a] Primary outcome.

[b] Secondary outcome.
[c] Exploratory outcome.

within their groups for magnetic resonance imaging. Group assignment will be completed using RedCap [28,29].

2.7. Safety monitoring plans

All data will be inputted to the REDCap database [28,29] by the research coordinator. Ongoing data audit/clean-ups will be conducted after the first 5 completed participants and then each subsequent 10 completed participants to ensure data accuracy. The study PI will be notified by the AIRC technologist about any atypical findings in participants that are randomized the undergo MRI. The PI will review the images with a radiologist and notify participants about any incidental clinically relevant findings. Confidentiality will be insured by assigning participants to a record ID and keeping their data stored under that record ID in RedCap. Additionally, any paper forms collected will be stored in a locked cabinet behind a locked door. Only the study team will have access to the data. Any disclosure of de-identified data will only occur after appropriate data use agreements in place with the study institution.

An independent data safety monitor, who is a physician board certified in Physical Medicine and Rehabilitation and Brain Injury Medicine, will meet with the study PI quarterly to review compiled data regarding enrollment, study completion and participant withdrawals, and adverse events reported. Adverse events and serious adverse events will be reviewed by the data safety monitor to determine whether they were related or unrelated to the study interventions. The data safety monitor will be able to unblind individual participant assignments if there are concerns that an adverse event was related to the individual gas mixture. The study will be stopped if on discussion between the data safety monitor and study PI, it is felt that risks of the study outweigh potential benefits. The study will be paused after 3 serious adverse events for the data to be reviewed and determine whether the study would be appropriate to continue.

Reasons for participants to be removed from the study include, but are not limited to: having a serious adverse event; becoming ineligible to participate, such as becoming pregnant, developing a medical conditions listed in the exclusion criteria, or requiring treatments that are not allowed in the exclusion criteria; being unable to clear the ears in the hyperbaric oxygen chamber; developing signs of middle ear barotrauma on otoscopy; not following instructions from the researchers; missing 5 sessions as the participant would not be able to complete the entire 20 session protocol within the planned 5-week period. Participants may also withdraw from the study at any time.

2.8. Statistical methods

2.8.1. Overall analysis plans

We will use the principle of intention-to-treat (ITT) analysis. Under this principal we will consider all study subjects as randomized in the beginning regardless of whether they receive the allocated treatment or not. In addition to ITT, we will perform the per-protocol analysis to assess the robustness of the results to protocol deviations. We anticipate that negligible number of patients will be lost to follow-up; therefore, we anticipate that both the analyses (ITT and per-protocol) should agree very closely.

In the event of follow-up losses, missing outcome measures will be carefully assessed. We will use complete case analysis in various scenarios:

1. When the observed proportions of missing data are below 5% (negligible)
2. When there are no identified auxiliary variables (those which not included in regression analysis but correlated with the parameters with missing values)
3. When missing data is missing completely at random (MCAR)

Little's test could be used to confirm whether the data is MCAR or not. Multiple imputation methods will be used if the proportions of missing data are observed between 5% and 40% and the missing data is not MCAR. Complete case analysis will be performed in case of substantial missing observation (higher than 40%) followed by a sensitivity analysis by conducting multiple imputation. However, in such a case we will discuss the interpretative limitations of the trial results and we will mention that the trial findings may only be considered as hypothesis generating findings.

Objective 1: To evaluate the efficacy of 20 sessions of 90 min HBOT (100% FiO2 at 2.0 ATA) compared with sham treatment to improve outcomes for adults with persistent PCS 3–12 months after mild TBI/concussion.

Aim 1 (primary aim): To determine if HBOT decreases symptom burden in persons with persistent PCS 3–12 months after mild TBI/concussion.

To evaluate the treatment effect, a linear random-intercept model (mixed model) analysis for repeatedly measured RPQ will be used to assess the between-group differences at the two consecutive follow-ups. The fixed effects of the statistical model will include the following: the baseline values of the outcome as a covariate, the main effects of the intervention and follow-up, the interaction term between intervention and follow-up (time), and the interaction term between the baseline value of the outcome and follow-up (time).

Aim 2 (exploratory aim): To determine if HBOT improves cognitive

Table 3
Timing of interventions and data collection.

Assessment	Treatments							
	Pre-Screening	Baseline	5	10	15	20	1-week post-treatment	1-month post-treatment
Rivermead Post-Concussion Symptoms Questionnaire (RPQ)	X	X					X	X
Medical Screening Form	X							
Review of Systems	X							
Physiatrist Virtual Visit	X							
Treatments			X	X	X	X		
Quality of Life (SF-36)		X					X	X
Cognition (NIHTB-CB)		X					X	X
Physical Function (NIHTB-MB)		X					X	X
Mood Symptoms (BSI)		X					X	X
Global Impression of Change (GIC)		X	X	X	X	X		X
Percent Back to Normal		X	X	X	X	X		X
MRI[a]		X					X	
Pregnancy Test		X						
Guess Group Assignment						X		

[a] Only 50 (25 in each group) of individuals will be randomized to MRI.

function in individuals with persistent PCS 3–12 months after mild TBI/concussion.

Linear random-intercept model (mixed model) analysis for repeatedly measured NIHTB-CB composite scores (crystalized and fluid separately) will be used to assess the between-group differences at the two consecutive follow-ups. The fixed effects of the statistical model will include the following: the baseline values of the cognition composite score as a covariate, the main effects of the intervention and follow-up, the interaction term between intervention and follow-up (time), and the interaction term between the baseline value of the outcome and follow-up (time). We will repeat such analyses for NIHTB subset scores (oral reading recognition, picture vocabulary, list sorting, picture sequence memory, pattern comparison, Flanker, and DCCS).

Aim 3 (secondary aim): To determine if HBOT improves quality of life in persons with persistent PCS.

A linear random-intercept model (mixed model) analysis for repeatedly measured QoL–SF–36 score, will be used to assess the between-group differences at the two consecutive follow-ups. The fixed effects of the statistical model will include the following: the baseline values of the QoL–SF–36 score as a covariate, the main effects of the intervention and follow-up, the interaction term between intervention and follow-up (time), and the interaction term between the baseline value of the outcome and follow-up (time).

Assumptions for all statistical methods will be examined with sufficient descriptive statistics. Results will be reported as mean differences with 95% confidence intervals (CIs) and P values at baseline and each follow-up time point. All the statistical tests will be performed based on a two-sided alternative hypothesis. A p-value of less than 0.05 would be considered statistically significant. Stata 17.0 MP - Parallel Edition (Copyright 1985–2021 StataCorp LLC, StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA) and/or R version 4.2.0 will be used for all statistical analysis.

Objective 2 (secondary objective): To assess the safety and tolerability of hyperbaric oxygen treatments and compliance with treatment in adults with persisting post-concussion syndrome.

Adverse events for both the treatment and sham groups will be collected using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Number of participants in each group with each adverse event will be reported.

Objective 3 (exploratory objective): To evaluate changes in brain perfusion and cerebral metabolic rate for oxygen utilization ($CMRO_2$) before and after 20 treatments and evaluate the association of these findings with symptom resolution.

Change in ASL from the pre-to post-treatment evaluation will be used to analyze the change in brain perfusion and change in $CMRO_2$ from the pre-to post-treatment evaluation will be used to analyze the change in global venous oxygenation following HBOT. To evaluate the treatment effect, a linear random-intercept model (mixed model) analysis for repeatedly measured outcomes will be used to assess the between-group differences of ASL and $CMRO_2$ at the two consecutive follow-ups. The fixed effects of the statistical model will include the following: the baseline values of the outcome as a covariate, the main effects of the intervention and follow-up, the interaction term between intervention and follow-up (time), and the interaction term between the baseline value of the outcome and follow-up (time).

3. Discussion

While concussion/mild TBI are common, there are no current specific treatments for concussion other than limited rest and symptomatic management. Persisting symptoms result in diminished productivity and quality of life. At the present time, there is not conclusive scientific evidence to confirm or refute the value of HBOT for treatment of persistent PCS; nevertheless, it is being used in spas and non-accredited free-standing centers with surprising frequency and at great personal costs.

The authors recognize that there is debate within the field regarding appropriate HBOT protocols and have designed a protocol that adheres to the rigorous standards set by the Undersea and Hyperbaric Medical Society (UHMS), which is the governing body for HBOT in the United States. Furthermore, this study will utilize a true placebo gas mixture with 10.5% oxygen and 89.5% nitrogen that mimics the same partial pressure of oxygen at normotoxic conditions when given at 2.0 ATA. Presently, there is no clear consensus on the most appropriate sham treatment protocol [30]. The placebo gas mixture utilized in this study allows for individuals receiving the sham and the treatment to be treated simultaneously within a multiplace chamber with full blinding of all study personnel that will be interacting with the participants during the treatment sessions as the sole person aware of the gas mixture is the HBOT technician, who only meets the subjects for initial orientation prior to randomization. Additionally, in this study, the population recruited will better reflect those in the general civilian population with excellent characterization of possible confounding variables. Lastly, we will seek to obtain objective measures of cerebrovascular function that may assist in identifying those subjects most likely to benefit from this type of treatment. The findings will be disseminated in journals related to care of persons with brain injury/concussion and hyperbaric medicine journals in addition to academic conferences. Authors will need to adhere to the ICJME guidelines for authorship and there are no plans to use professional writers. The dataset will not be available for public use.

In conclusion, the HOT-POCS Study will answer many questions on whether HBOT can improve persistent post-concussive symptoms in those 3–12 months post-injury and improve objective measures of cerebrovascular blood flow and oxygen metabolism. Findings from this study will be disseminated in accordance with the CONSORT 2010 reporting guidelines for pilot and feasibility trials [31,32].

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Protocol

Protocol version 2. Any amendments to the protocol will be submitted to the study IRB and clinicaltrials.gov.

Roles of contributors

RG and SP will be responsible for overall project oversight, dissemination of research findings, and adherence to study design. JB and RG will provide oversight and assistance with the HBOT versus placebo intervention. BT will provide statistical analysis for the project. CK and JM will be responsible for participant recruitment, data collection, and data management. All authors will be responsible for research preparation and dissemination. RZ will provide oversight for the imaging portion of the study.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Funding for the study was supported through the Texas Health Resources Foundation and O'Donnell Brain Institute. The authors do not have any personal relationships or financial interests to disclose.

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protocol is registered at clinicaltrials.gov (#NCT05643482). The authors/study-investigators have no competing financial or non-financial conflicts of interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101176.

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