Application of hyperbaric oxygen therapy in traumatic brain injury

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Content

Background and epidemiology:

Traumatic brain injury (TBI) is defined as damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, orprojectile penetration.The major causes of TBI in high income countries are motor vehicle crashes (50%), falls (38%) and violence (including attempted suicide) (4%) (1). TBI has become a major public health concern worldwide for both civilian and military populations.At least 10 million new head injuries occur annually worldwide, and these account for a high mortality rateof deaths in young adults (2). The annual incidence in the United States, for example, is estimated at 1.4 million people. Of these, 50,000 will not survive the acute injury, 235,000 will be hospitalized, and the remaining 1.1 million will be treated and discharged from emergency departments. Data are lacking on patients who have TBI evaluated in nonhospital settings or did not receive any medical care (3). These data do not include the military or veterans administration systems (4). In addition, patients whose TBI is secondary to sports-related injuries and do not seek medical attention may also add up to 3.8 million cases of unaccounted patients each year (5). TBI is noted to be the signature injury of the Afghanistan and Iraq military conflicts: 28% of the soldiers evacuated have TBI. There are no accurate statistics on mild TBI because most people don’t go to a hospital,and 25% of those who do are never re-evaluated beyond the time of injury(6).According to the Center for Disease Control, more than 5 million Americans, or about 2% of the population, are living with long-term disabilities resulting from TBI(7, 8).

The health implications of TBI are multi-dimensional, dependent on the severity of TBI, and have a wide spectrum of physical, mental, social, and emotional disabilities. TBIalso presents a considerable financial burden on individuals, families and national economies and health systems, with annual costs estimated at more than $56 billion(8).

Clinical presentation:

TBI classificationis usually based on severity, anatomical features of the injury, and the cause of the injury. The severity is assessed according to the loss of consciousness (LOC) duration, the post-traumatic amnesia (PTA), and the Glasgow coma scale (GCS) grading of the level of consciousness.

About70–90%of the TBI in the US are classified as mild TBI (mTBI) or concussion: LOC duration of 0–30 minutes, PTA duration of less than a day and GCS grade of 13–15(9). Post concussion syndrome (PCS) is a set of symptoms succeeding mTBI in most patients. The PCS symptoms include headache, dizziness, neuropsychiatric symptoms (including behavioral and mood changes, confusion), difficulty balancing, fatigue, changes in sleep patterns and cognitive impairments (including memory, attention, concentration and executive functions disorders)(10, 11). PCS may continue for weeks or months, most patients recover butup to 25% of the patients may experience prolonged PCS (PPCS) in which the symptoms become chronic and last for over six months(12-15).

The remaining10-30% of TBI are classified as moderate to severe if one or more of the following criteria apply: death, loss of consciousness of 30 minutes or more, PTA of 24 hours or more, and the worst GCS full score in the first 24 hours is <13 providedthat this is not invalidated by other factors such as intoxication or sedation. In addition if there is evidence of injury in imaging, such as hematoma, contusion or hemorrhage then the TBI would be in the moderate-severe category (9). Patients with moderate-severe TBI may present with severe headaches, repeated vomiting or nausea, convulsions, diverse levels of consciousness, anisocoria, dysphasia, dysarthria, weakness or numbness in the limbs, loss of

coordination, confusion, restlessness, or agitation. The mortality rate in this group is up to 40% and survivors usually suffer from significant physical disabilityon top of cognitive, psychological and emotional impairments(16).

Pathophysiology:

The pathophysiology of brain injury has primary and secondary components. At the time of impact the neurological tissueenduresa variable degree of irreversible damage (primary injury).Primary injuries include contusions, lacerations, diffuse axonal shear injury, diffuse vascular injury and shearing of cranial nerves (17).Diffuse axonal injuryis the hallmark lesion in TBI. The deceleration and acceleration forces most often associated with rotational forces cause axonal shear-strain, which results in cytoskeletal malalignment and permeability modifications. The shear-strain is more likely to develop in areas between tissues of different densities and viscosities. ***The microscopic extent of injury always exceeds the macroscopic abnormalities.*** The most frequent location is at the gray-white matter junction in the frontal and temporal lobes (18-20).

Following the primary injury, a chain of events occurs in which there is ongoing injury to the brain through edema, hypoxia and ischemia secondary to raised intracranial pressure (ICP), metabolic changes, infection, hydrocephalus, release of excitotoxic levels of excitatory neurotransmittersand impaired calcium homeostasis (21, 22).

Standard management and outcome

In the acute phase of TBI, therapy focuses on minimization of secondary injury by ensuring adequate oxygenation, hemodynamics, control of intracranial pressure, and strategies to reduce cellular injury(21, 22). Penetrating injuries or mass lesions such as intracranial hematomas are usually removed surgically. A number of therapies such as barbiturates,

calcium channel blockers, mannitol, steroids, anti-convulsants, hyperventilation andhypothermia have been tried and none hasshown unequivocal efficacy in improving prognosis(23-27).Moreoverdifferent centers use a different treatment plans and there is suboptimal compliance with current evidence-based practice guidelines for moderate-to-severe TBI patients (28-30).

Currently, there is no effective treatment/metabolic interventionin the daily clinical practice for post TBI patients with chronic neurological dysfunction. During the subacute-chronic phase, patients participate in intensive rehabilitation programs thataim to improve independent function and quality of life, mostly by helping the patients to adapt to their disabilities. Rehabilitation includes a multidisciplinary approach thatmay include physiotherapy, speech and language therapy, cognitive rehabilitation therapy, medications and others (31). However, several systematic reviews found limited evidence to support the efficacy of rehabilitation programs (32). Approximately 60% of TBI patients survive the acute injury. Out of those, 45-50% remain withmoderate disability and 10% withsevere disability. Many long term outcome studies concluded that patients with moderate-severe TBI show physical and functional improvement but remain with cognitive,emotional andneuropsychosocial impairments. Patients demonstrate significant limitations in daily living tasks(33-36).

As stated above, 25% of PCS patientsdevelop chronic long term disabilities (PPCS) (12-15). Patients treated for PCS receivevarious off-labelpharmacologic and psychotherapeutic interventions to address co-morbidities such as depression, but no medication has been approvedbythe united states food and drug administration (FDA for treatment of any neuropsychiatric consequences of TBI (37). Rehabilitative therapies are selected to address symptoms persisting after injury, including physical visual and vestibular therapies. Patients are encouraged to participate in support groups to address cognitive symptoms (37).

Rationale for HBOT use

The brain receives 15% of the cardiac output, consumes 20% of the total body oxygen, and utilizes 25% of the total body glucose. The energy thus supplied is only sufficient to keep about 5-10% of the neurons active at any given time. At a standard healthy condition, the brain utilizes almost all the oxygen/energy delivered to it.

In the acute phase, hypoxia following TBI is an integral part of the secondary injury described above. The anaerobic metabolism utilized byhypoxic neurons results in acidosis and an unstable reduction in cellular metabolic reserve(38). As the hypoxic state continues, the neurons lose their ability to maintain ionic homeostasis and become prone to cell membrane degradation. Eventually, irreversible changes result in cell death(39).And even without cell death metabolism is reduced in the hypoxic microenvironment and the decreased neuronal activity leads to loss of synapses and hampered neuronal connectivity (40).

HBOT can increase oxygen availability in the early period following TBI, reduce secondary injury and improve the long term outcome(41-45). Improved brain tissue oxygenation has been shown to improve aerobic metabolism and decrease brain lactate concentrations in animal models (46, 47)as well as in patients withsevere TBI (48-50).

HBOTalso improves cerebral vascular flow (48, 51-53), promotes blood-brain barrier integrity, preserves mitochondrial membrane properties(44), reduces inflammatory reactions (54), reduces both microgliosis and astrogliosis reactions(55, 56), decreases the lesion size (42, 44) and brain edema,and reduce intracranial hypertension(42, 57, 58).

In the subacute-chronic delayed stage,previous animal studies have revealed the beneficial effect of HBOT on the chronicallyinjuredbrain tissue and on the resultant cognitive dysfunction in animal models (43, 53, 59).The elevatedoxygen concentrationin the blood and

injured tissue during treatment (47, 57, 60) can supply the energy needed for the processes ofneuroplasticity.

HBOT induces neuroplasticity by stimulating cell proliferation (61), promotes neurogenesis of endogenous neural stem cells (62), regenerates axonal white matter (63), improves maturation and myelination of injured neural fibers (64, 65), and stimulates axonal growth thus increasing the ability of neurons to function and communicate witheach other (66, 67). At the cellular level, HBOT can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function (in both neurons and glial cells)(68 ,62 ,57). Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells, including astrocytes (69). The common denominator to all repair and regeneration mechanisms is that they are all oxygen dependent.

HBOT was also found to have a significant role in initiation and facilitation of angiogenesis,which is requiredfor axonal regeneration(70-74). Local or diffuse hypoperfusion, as in TBI,is a limiting factor for any regenerative process(75-79). By inducing angiogenesis, HBOT improves the cerebral vascular flow necessaryfor neurogenesis and synaptogenesis (80, 81).

Evidence-Based review of HBO use

Acute and subacute TBI

Therewere8 randomized controlled trials (RCT)(Holbach's 1974 article in German was not covered), one meta-analysis and one prospective study evaluating the clinical effects of HBOT in patients suffering from TBI in the acute and subacute settings.The studies had different HBOT protocols of time to treatment (several hours to 30 days), hyperbaric pressure (1.5-

2.5ATA), dose of treatment (60 minutes daily to 10 sessions a day), number of sessions (3-40) and follow-up evaluation (days to 1.5 years).All RCTs compared a standard intensive treatment regimen to the same treatment regimen with the addition of HBOT. Only closed-head injuries were included.

The studies used mostly Glasgow coma scale (GCS) and Glasgow outcome scale (GOS) to evaluate the clinical effects. Several studies analyzed the scores as continuous parameters rather than nominal groups of favorable and unfavorable outcomes. In addition, several studies do not factor the result per severity of injury at baseline.

Low level evidence:

Parkash'sRCT(82) on 56 children (28 treated by HBOT) with severe TBI, treated 10 days post injury, reported significant improvement in GCS score (14 vs. 10 after 3 weeks). However, HBOT protocol was not revealed, GCS was referred to as a continuous parameter rather than nominal groups, and p-values were not supplied. These allconsiderably diminish the validityof this trialresults.

Mitani's case series(83) reported some benefit depending on the type of brain injury: improvement in acute subdural hematomas and mild to moderate diffuse axonal injuries andpoor outcomes insevere diffuse axonal injury. However, in addition to the retrospective nature of this data, the statistical analysis is lacking and the HBOT protocolis unclear.

Lee et al. case report (84)described a significant complication ofHBOT in the acute trauma setting:tension pneumocephalusthatmandated emergent surgery. Hence unrepaired skull base fractures and CSF leaks weresuggestedas contraindications.

Moderate/high level evidence:

The largest randomized controlled trial (RCT) in severe TBI patients, conducted by Rockswold(85), included 168 patients (84 treated by HBOT) and demonstrated a significant reduction inmortality rate (17% vs. 32%, p=0.037). Further analysis showed reducedmortality

was mainly in patients with initial GCS of 4-6 (p=0.04) as well as patients with intracranial pressure higher than 20mmHg (p=0.02). It should benoticed that intubated patients without myringotomy increased (rather than decreased)ICPduring HBOT. Even though mortality was reduced, in those who survived there was no change in favorable clinical outcome. This trial had the most intensive protocol of HBOT, with 3 sessions of 60 minutes per day. In later studies done byRockswoldgroup, the HBOT protocol was changed with significant reduction in the frequency/intensity of treatment.Myringotomy, which eliminated the ICP elevation during HBOT,was included inthe treatment protocol.

In a later RCT (86), Rockswold focused on brain metabolism and oxygenationrather than the clinical effects in 69 patients (26 treated byHBOT) with severe acute TBI (86). The HBOT treated group had significantly increased tissue oxygenation ($p<0.003$), cerebral blood flow ($p<0.01$) and cerebral metabolic rate ($p<0.01$).The improved aerobic brain metabolism was reflected bydecreased lactate and lactate/pyruvate ratio. The beneficial metabolic effects lasted 5-6 hours post HBOT session, while decreased intracranial pressure ($p<0.001$) was noticeable even24 hours after thesession. As stated earlier, this study did not evaluate anyclinical status as primary or secondary outcome.

In a later RCT by Rockswold(87) thatincluded42 patients (22 treated byHBOT) with severe acute TBI,HBOT significantly decreased mortality by more than 50% (16% vs. 42%, p=0.04) and increased the proportion of favorable outcome measured by GOS six months post injury in the HBOT treated group (74% vs. 38%, p=0.02). HBOT also decreased intracerebral pressure ($p<0.0006$), increased brain tissue oxygenation ($p<0.00001$) and improved aerobic metabolism with low lactate/pyruvate ratios ($p<0.0078$). In this trial, each HBOT session was followed by 3 hours of normobaric 100% oxygen treatment.

Ren’s RCT (88)included55 patients (35 treated byHBOT)suffering fromacute TBI. The results clearly demonstrated statistically significant improvementin GCS score (5.1 to 14.6, $p<0.01$)

as wellas significant improvementin unfavorable outcome measured by GOS within 6 months post injury ($p<0.01$).There werealso a significant reduction in abnormal brain activity ($p<0.01$), improved brain perfusion and decreased cerebral vascular resistance ($p<0.01$)(89).It should be noted thatGCS was used as a continuous parameter and mortality cases were excluded from the study.

RCT by Mao et al. (90)included 60 patients with acute TBI (30 treated byHBOT).The results of the study demonstrated significant improvement in both GCS ($P=0.05$) and GOS ($P=0.01$) at 30 and 90 days post treatment. It should be noted thatscores were referred as continuous parameters instead of nominal groups.

Lin et al. randomized(91)44 patients within 22-32 days from injury (subacute TBI), where the HBOT group (22 patients) achieved statistically significant better GCS scores than the control group 3 and 6 months after treatment ($p<0.05$). Statistically significant improvement was recorded for patients with GOS=4 at baseline ($p<0.05$).No significant differences were noticed between most severely injured groups of patients, stratified to GOS 2-3.It should be noted that the study lacks analysis of outcome per severity of TBI and nominal groups of GCS instead of a continuous parameter.

Xie et al.'s RCT (92)included60 patients with acute TBI (30 treated byHBOT). The study results demonstrated statistically significant improvement in GCS score with relation tostandard neurosurgical care($P < 0.01$).It should be noted that GCS scores were used as continuous parameters inadequately and there was no analysis of severity of TBI.

RCT in the late 70's by Artu(93)included60 coma patients with acute TBI (31 treated by HBOT).Whileoverall mortality and mean duration of coma werenot changed by HBOT, further analysis revealed that the subgroup of young patients with brain stem contusions had statistically significant higher rates of recovered consciousness at 1 month ($p<0.03$). The main drawback in the study was the HBOT protocol which was inconsistent.

Meta-analysis done at 2012 (94) pooled 7 randomized controlled trials (not including the 2013Rockswold's RCT mentioned above) and concluded that HBOT resulted in significant reduction of mortality, preventing 1 death for every 7 patients treated (CI 4-22), and GCS improvement of 2.68 ($p<0.0001$). However,no significant improved functional outcome was reported in those who survived even though a clear trend was demonstrated ($p=0.07$). It should be noted that those trials that did not assess functional outcome properly wereexcluded from that analysis. In addition, in several studies, GCS was referred to as a continuous parameter rather than nominal groups.

A prospective study done by Mogami(95)included 51 TBI patients and showed neurological improvements in 50% of the patients during hyperbaric exposure. 33% had remarkable improvementwhich included restoration of mental and neurological function. In addition,EEG abnormalities decreased in 33% of the patients. Cerebrospinal fluid pressure decreased considerably during treatment and reverted rapidly during decompression. No statistical analysis or severity of injury was given.

Normobaric oxygen was also evaluated in the setting of TBI. Diringer et al. prospective study on 5 patients did not find changes in brain metabolism and CBF when normobaric oxygen of 0.5 FiO_2 was provided (96). Tisdall et al. prospective study on 8 patients showed normobaric oxygen for 1 hour can improve brain metabolism, brain oxygenation but no changes were reported in ICP (97). Vilalta et al. prospective study on 30 patients revealed that normobaric oxygen for 2 hours can improve brain metabolism (reduced lactate/pyruvate and increase in glucose) in patients with anaerobic metabolism present prior to intervention (98).

Adverse effectsduring the acute setting of traumatic injury: Two studies reported including patients with acute TBI reported that 13% of the patients had chest x-ray infiltrates. These chest infiltrates can be attributed to the acute setting of traumatic injury (chest injury or ventilator associated pneumonia in those who required mechanical ventilation). Only one trial assessed CNS oxygen toxicity, which occurred in two (2.3%) of the patients. Middle ear barotrauma was reported in two patients (2.3%) in one trial (94).

In summary, in the acute setting meta-analyzing the data is difficult due to the variety of treatment protocols and evaluation time points. However, HBOT in the acute-subacutesettingafter TBIimproves both clinical and metabolic outcomes. Mortality wassignificantly reduced in all studies that used it as an end point. As for favorable functional outcomes, exceptforRockwold's series with 3 daily sessions, allstudiesdemonstratedsignificant improvementeven though more severely injured patients survived in the HBOT treated groups.

Chronic TBI:

There were 5 randomized controlled trials (RCT), 4 prospective studies and 4 cohort studies evaluating the clinical effects of HBOT in patients suffering from TBI in the chronic stage. The studies had different HBOT protocols for hyperbaric pressure (1.2-2.4ATA), severity of injury (mild-severe), number of sessions (40-120) as well as different methods of evaluation (PCS scales, PTSD scales, cognitive scores, SPECT and others). All RCTs showed that HBOT treated groups improved significantly compared to the pre-treatment score. The main issue in the RCTS is setting a proper

control group. Low dose hyperbaric pressure (such as 1.3ATA) has significant physiological effects and therefore cannot and should not be considered as sham but rather as low dose treatment. It was clearly demonstrated that low dosage (1.3 ATA), when used on the control group, had significant beneficial effects. When a standard TBI treatment was compared to HBOT, the beneficial effect could be properly evaluated and clearly demonstrated both by clinical and bio-imaging end points. Since there is no standard for evaluation (such as GCS in the acute TBI), the studies used different measures of cognitive and neuropsychological evaluations which are hard to compare.

Low level evidence:

Tal et al. evaluated 10 patients with PPCS due to mTBIin whom symptoms lasted more than6 months since the acute injury (99). Significant improvement in cognitive functions (p=0.007) was demonstrated using computerized evaluation. Perfusion MRI showed significantly increased cerebral blood flow and cerebral blood volume. Study limitations: a relatively small sample and lack of control group.

Sanhiet al. performed retrospective analysis (100) of 40 patients (20 treated by HBOT) of which some weresubacute and some chronic severe TBI cases. A significantly higher improvement in cognitive functions measured by Ranchos Los Amigos scale (RLAS) (50% vs. 25%) was noticed in the HBOT treated group. HBOT treated patients who were ina vegetative state hadthe highest improvement in disability rating scale (DRS) (40% vs. 20%). Patients treated within 1-6 months post injury hadthe highest proportion of recovery. Study limitations: in addition to the retrospective analysis nature of this study, the inclusion criteria were unclear, grouping of patients in final scores and p-values were not reported.

Churchill published a prospective study (101) thatincluded 28 patients sufferingfrom severe TBI for at least 1 year. Even thougha year or more had elapsedsincethe acute insult, HBOT induced improvement in symptoms (51% memory, 51% attention/concentration, 48% balance/coordination, 45% endurance, 20% sleep). However, on standardized evaluations of cognition and questionnaires no significant changes were reported.A small subset of the patients had brain imaging,and of those more than 50% showed significant improvements in brain perfusion. The study has several limitations due to the small sample size, vague inclusion criteria and no control group. In addition, the statistics were calculated for the entire group of chronic brain injury and not specificallyfor post TBI patients.

Shi et al. (102) prospectively evaluated 310 patients with PCS or epilepsy and a history of trauma at least 1 month prior to inclusion. Post HBOT brain SPECT showed normalization of 50% of the perfusion defects. 70% of the patients had significant improvement in clinical symptoms. This is the second largest cohort reported thatencourages the use of HBOT.However, it has several methodological flaws. 1)The inclusion criteria werevague, and the inclusion of seizuresimpairs the validity of the results as seizures are usually caused by more severe degrees of trauma. 2)The severity of trauma was not consideredas epilepsy is usually caused by more severe degrees of trauma. 3)Thestatistical analysis was not satisfactory.4)There was no control group. 5)The clinical improvement was not well validated.

Harch et al. reported a case series(103) of 16 patients with military background and mild-moderate TBIfor more than 1 year prior to injury. 80% of the patients reported improvementwhereas all the patients had improved physical examination. In addition, there was a statisticallysignificant improvement in the cognitive functions tests:IQ ($p<0.001$),

working memory (p=0.003), Stroop test (p<0.001), memory (p=0.02), TOVA impulsivity (p=0.04). The patients had a significant improvement in psychological scores: PTSD (p<0.001), Rivermead PCSQ (p=0.0002), anxiety (p=0.007), depression (p<0.001). There was a significant Improved quality of life (p=0.003). Brain metabolism was evaluated by SPECT and increased perfusion/activity in white matter and several gray matter areas (p<0.01) was demonstrated. The use of imaging alongside cognitive and psychological evaluations is valuable in demonstrating the neuroplasticity effect of HBOT. The study was designed as a pilot study, and as such had obvious limitations of small sample size, lack of control group and the mix of few moderate TBI with mild TBI patients. In addition, the use of Rivermead PCS scale is problematic as discussed above. Half of the patients were active military servicemen and might have been biased due to potential secondary gain from reporting illness (gaining compensation). Nevertheless, this is one of the few and important studies capable of showing an improvement in military service soldiers. In Israel this cohort of soldiers is not included in a prospective study due to ethical reasons (since soldiers are used to obey orders/request the validity of the informed consent is questionable) and possible secondary gain from reporting illness.

Ly LQ et al. series (104)included6 patients who suffered from paroxysmal sympathetic hyperactivity after severe TBI unresponsive to accepted measures. Symptoms improved after HBOT. Since this is only a small size case series with no control group the evidence level is relatively weak. Yet, it sets the perspectiveof additionalphysiological effects of HBOT.

Wright et al. reported on a case series (105)of 2 military servicemen with PCS induced 6 months prior to treatment. The patients reported improved symptoms,and theirautomated neuro-psychological assessment showed improvement up to pre-injury levels. As a case series of a very small sample, itsevidence level is very low. Nevertheless, this is yet another of the few reports of military men whose symptoms of chronic PPCS improved after HBOT.

Barrett KF performed a non-randomized prospective study (106)on 10 patients who had sufferedtrauma3 years prior to inclusion. The study did not find significant objective changes in neurologic and neuropsychometrictests norany consistent pattern of perfusion changes over time in SPECT. The limitations of this study are the sample size and vague inclusion criteria.

Harchreported(107) on a military service veteran with chronic PCS and PTSD who experienced improved clinical symptoms and brain perfusion in bilateral frontal and temporal areas.

Hardy reported(108) on a patient with neurological symptoms due to injury 1 year earlier. After HBOT, there were improvements in both sensorimotor and neuropsychological symptoms, and EEG showed enhanced P300 amplitude in the damaged area. A year after treatment the patient symptoms relapsed, and after another series of HBOT sessions the improvements were reinstated. Despite being a case report it is worth noting as it suggests that some patients may experience relapseand would benefit from additional therapy.This is also the only report on EEG changes with HBOT used for PPCS patients.

Wooley et al. reported a case (109)ofpostural instability and walking difficulties due to severe TBI 2 years prior to intervention. Mild improvement was gained right after HBOT but was not evident 6 weeks later. The lack of anatomical and functional imaging may have been the key to failure in this case.

Neubauer et al. reported on a patient who suffered severe TBI 1 prior to HBOT. Post HBOT, the patient had improved motor and cognitive functions as well as normalized perfusion in SPECT scans. The use of concurrent functional imaging strengthens thevalidity of the observed clinical effect. Notice that this patient received one of the largest number (188) of sessions in the literature.

A case reportof a patient with chronic neurological deficits due to severe TBI by Lee et al. suggested that tension pneumocephalus is a rare complication that may occur in unrepaired skull base fractures(110).

Moderate/high level evidence:

Wolf's double-blind RCT on 50 military servicemen(111)suffering frommild TBI symptoms compared HBOT of 2.4 ATA to "sham" treatment of 1.3 ATA. Both groups showed considerableimprovement in post-concussion symptoms and in the PTSD symptomsquestionnaire (p=0.001).However,there were no differences between the groups (p=0.35 for PCS questionnaire and p=0.84 for PTSD questionnaire). Even though the study had a sham control group and double blinding was applied, it had several methodological pitfalls,and its equivocalinterpretation of the findings calls for further discussion. First,the use of 1.3 ATA as sham treatment is a known dilemma in hyperbaric medicine. The only way to administer placebo pressure is to increase the environmental pressure to an extent that patients feel it in their ears. Alas, even at 1.3 ATA of compressed air there is a significant increaseinplasma and tissue oxygen pressure by at least 50%. It is well known that any slight increase in the partial pressure,say 1.05 ATA (at the Dead Sea), can bring on significant physiological effects (112, 113). Thus, the evidence that both groups improved considerably beyond what would be expected 6 months or more afterinjury may be related of a non-sham treatment. 1.3 ATA may well serve as a low dosageeffectivetreatment rather thansham control. The 2.4 ATA may even be less effective than1.3 ATA due to inhibitory effects ofvery high oxygen levels in the tissues.

Furthermore, military patientsintroduce a majorpitfall asthis cohort has secondary gain in the form of financial compensation fortheir disability. The study was funded by the US department of Veterans Affairs (VA) and Department of Defense (DoD) and the patients were

asked to report about the symptoms by a self-assessmentquestionnaire. No objective end points such as metabolic imaging of the brain were used, and all conclusions were based on those questionnaires. With regards to the study cohort, the diagnosis criteriawere based only on subjective reports and not on clear identification of biological brain damage, such as MRI/PET-CT or SPECT.Thus, patientswith symptomatic PTSD could have been included without any direct brain mechanical injury.

In summary, the authorsmay havereachedthewrong conclusions for the following reasons:

- Room air at 1.3Atm cannot serve as shamcontrol since it is not an“ineffectual treatment”. This treatment leads to a significant increase in the level of tissue oxygenation which has been shown to be effective (114, 115).
- 100% oxygen at 2.4Atmmay give rise to oxygen levels high enough to causean inhibitory effect or even focal toxicity.
- The diagnostic criteria were not based on clear, direct demonstration of brain damage by brain imaging (MRI, PET-CT or SPECT).
- Soldiers may have secondary gain from reporting illness, which is a source of bias in a study whose end points are based on subjective self-assessment.

Cifu’sRCT(116, 117), also funded by DoD-VA, was conducted on 61 active military servicemen with PCS symptoms for at least 3 months. They were divided into 3 groups withdifferentFiO2(75%, 100%, 10.5%) at 2 ATA simulating 1.5 ATA HBOT, 2 ATA HBOT and no HBOT. The study did not find any significant differences(other than few items in group 2 and group 3) in cognitive functions ($p>0.05$), PCS (RPQ questionnaire $p=0.41$), eye-movements ($p>0.05$ for all measures) between the HBOT groups and the so called "SHAM group".

Cifu’s study may have been double blind, butitsmany drawbacks,similar to those of the study byWolf et al., render it quite unsuitable as a source of consistent, meaningful information. In addition to the above-mentionedones (secondary benefit from reporting illness, lack of objective measures of brain damage, and non-neutral "sham”) it should be noted that the soldiers included were treated with high doses ofseveralpsychiatric drugs, much more than usually expected in civilians suffering from PPCS.There is also the problem of relocating the soldiers to a high altitude base. With regards to the study end points, the use of Rivermeadpost concussion symptoms questionnaire has severalflaws in implementation as well as in reflecting the severity of the PCS. Because many of the cognitive tests performed do not have a second version for retaking (such as WAIS), a learning effect would have been expected in the post treatment evaluation. As in the previous study, co-morbidities such as PTSD or depression were not excluded.

Miller et al. RCT(118), funded by the DoD-Va, 72 active military servicemen with PCS from mTBImore than 4 months prior to inclusion, divided into 3 groups: HBOT at 1.5 ATA,"sham" (low pressure) of 1.2 ATA breathing air, and a standard TBI care group. The study reported significant improvements in both HBOT and sham groups in post concussion symptoms and neuropsychological symptoms (p=0.008 in HBOT and 0.02 in "sham") andno improvement in the TBI care group. Actually, The TBI care group showed worsening compared to the sham and HBOT groups. However, there were no significant differences between the HBOT and "sham"/low pressure groups (p=0.7). This study re-confirms that any hyperbaric pressure above 1 ATA cannot serve as sham intervention. Theauthors,however,interpreted the findings as indicating that the chamber serves as a placebo effect inducer. It should be noted that the subgroups in this studywererelatively small (22-24) for comparison between groups. In addition, as in the previous DoD-VA studies, the subjects were (a) military men with obvious secondary gains; (b) relocated to a high altitude site. The RPQ questionnaire with its

methodological problematic issues was used as the primary outcome indicator and no objective brain imaging were done.

Boussi-Gross et al. RCT(119)included56 patients with PPCS 1-6 years after the acute insultina crossover design protocol. The study used objectivecomputerized cognitive tests with well validated different versions for reliable test-retest comparison. The HBOT group showedsignificant improvements in all cognitive functions: memory ($p<0.0005$), executivefunctions ($p<0.0005$), attention ($p<0.005$), and information processing speed ($p<0.0001$).The control group had no significant change in any of the parameters ($p>0.2$). Then, when the control group was crossed to HBOT, they showed statisticallysignificant cognitive improvements ($p<0.05$) similar to thoseof the HBOT group ($p>0.4$).The same pattern was seen in the quality of life score. The study included objective metabolic brain imaging of the brain(SPECT)that clearly demonstrated increased brain activity after HBOT, andthe increased brain activity correlated with the cognitive improvement. This is the only RCT which had a control group thatwas not treated witha "low dosages sham". The crossover design affordeda triple comparison for proper evaluation of the HBOT effect. The major limitation in this study was the selection of patients by their brain SPECT,which may not always be feasible for all. However, this limitation and the results of this study should guide the proper use of HBOT on selected PPCS due to mTBIthat have a well defined metabolic brain injury.

Golden Z et al. prospective study (120) included 63 patients, of which 21 had chronic brain injury for more than 2 years. They were compared to 42 untreated, injured and normal patients.The study reported significant improvementsin all neuropsychological parameterscompared to the control ($p<0.0001$). The main limitations of this study werethe vague inclusion criteria and definition of chronic brain injury, that not all patients had injury induced by clear TBI, and that the HBOT protocol was not clearly defined. It should be noted

thatthe control groupreceived more therapeutic interventions than usually appliedin order to minimize the so-called placebo effect suggested by theDoD group.

Shi et al. RCT (121)hadthe largest cohort of patients with chronic TBI (320 patients, of which 195 were treated with HBOT). The study found significant difference in favor of the HBOT with relation to recovery fromclinical symptoms, control of seizures, and resolution of hydrocephalus ($P<0.01$). Unfortunately, the study has vague inclusion criteria as well as insufficient statistical analysis.

Adverse events during the delayed chronic stage: Most studies did not report any significant side effects. In Harch study(103), there were 5/16 cases of mild reversible middle ear barotrauma, where 4 of them were due to upper respiratory infection. One patient experienced mild bronchospasm due to low-humidity oxygen in the monoplace.

In a recent study, accepted to be published in April 2016 (in press), neurological patients (including PCS) had similar rate of adverse effects (barotrauma and oxygen toxicity) as seen in non-neurological patients.

In summary, meta-analyzing the data is complexdue to the variety of treatment protocols and different methods of evaluation. There have been several RCTs but most of them hadconsiderable methodological flaws. The few studies that weredone with a proper control group, appropriatecohortwithout secondary gain and objective measurable endpoints showed significant improvement in cognitive function, psychological aspects, quality of life,and brain metabolism.

Based on the currently available data, the following aspects should be address while selecting the appropriate patients and appropriate HBOT protocol:

- **Patients selection for HBOT**

  - ***Acute-subacute TBI:***

    Most studies in the acute-subacute settings evaluated moderate-severe TBI. Therefore, only moderate-severe TBI patients canbe selected for HBOT in the acute-subacute setting (first day up to 1 month afterinjury). There is no evidence regarding the optimal time to HBOT. However, considering the pathophysiology of secondary injury, patients should be treated as soon as they are medically stable for treatment in a chamber. Currently, there is not enough evidence for the specific sub-types of injuries that can get the most gain from HBOT. The main exclusions which should be considered in these patients would be CSF leak and base of skull fractures, which may increase complications rate.Adequate on-site professional medical stuff and equipment is a must for proper care of ventilated patients within the hyperbaric chamber.

  - ***Chronic TBI:***

    Most of the studies in the chronic setting evaluated mild-severe TBI patients with PPCS, and HBOT started 6 months to several years post injury. The data in the 1-6 months period is lacking. Since mTBI can resolve in the first few months, it may be justified to withhold treatment in this period until PCS is considered PPCS.

    The correlation of SPECT and clinical outcome promisesbetter results and affords objective evaluation of the patients.Therefore, patients should have brain SPECT performed, and be selected for treatment only if they demonstrate considerable metabolism defects.

- **HBOT protocol**

- ***Acute TBI:***

The best evidence for HBOT protocol in the acute-subacute settings was gleaned fromRockswold et al. The protocol was changedfrom 3daily 60 minute sessions with 100% oxygen at 1.5 ATA to 1 daily60 minute session of100% at 1.5 ATA followed by 3 hours of normobaric oxygen with better outcome. The use of higher pressures, such as 2 ATA or 2.4 ATA,isless common andcan't be shown to be preferable without direct comparison between the protocols. Until evidence shows otherwise, the protocol of choice should be the one easier to perform.

Currently, there is not enough evidence regarding optimal number of sessions (3-25 sessions). In the authors' opinion, due to the complexity of transfers to the chamber, 1daily session should be the standard and may be extended based on physicians' judgment according to theclinical progress, with a minimum of 3 daily sessions.

Myringotomy should be performed in all patients in order to avoidICP elevation during the treatment.

- ***Chronic TBI:***

Most evidence for HBOT in the chronic PPCS setting was gained with a protocol of 40-60 daily sessions of60 minutes at 1.5 ATA. Higher doses (2ATA, 2.4 ATA) were not proven beneficial, but the evidence is inconclusive as the relevant studies were poorly designedEven thoughlower pressure, such as 1.3 ATA, can also be effective, at this point in time we have more reliable data available on 1.5 ATA, and the safety profile of 1.5 ATA is considered very high.

The optimal number of sessions for specific patients is not clear. 40-60 sessions were used in the different study protocols,and in the authors' opinion 40 daily sessions

should be the minimumand 60 should be the recommended number for most patients, if feasible.

It is highly recommended that all patients should undergo brain SPECT evaluationformetabolism defects beforeand after thetreatmentperiod. This may serve as an adjunctive tool for the decision whether to continue the treatment further.

Cognitive evaluationsshould be standardized, with preference to automated objective evaluations. Tests should have several versions with high test-retest reliability.

Cost impact:

- ***Acute-subacute TBI:***

*Financially:*A previous cost-benefit analysis in TBI(122) showedthat the medical and societal costs per patient depend on the GOS of the patient: GOS 4-5 adds upto $54,000, GOS 2-3 to $200,000, GOS 1 to$1,053,000.

Thesuggested protocol of aminimum of 3 treatments at1.5 ATA for 60 minutes, depending onthe special needs and complexity, would sum to $3,000-20,000.

Compared to other medical interventions not proven in prospective clinical trials (surgery, hypothermia, Factor VII, and others) in the setting of acute TBI, this is one of the most cost-effective treatments that can be offered.

Medically: Based on the currently available data,7 patients need to be treated in order to prevent 1 death. The reduced mortality is in addition to the clinical benefit for those who survive.HBOT is safe, with a complications rate of2-3%. Since all patients should have myringotomy performed prior to HBOT, the risk of sinus and ear barotrauma is basically non-existent. There is a risk for lungs barotrauma of ventilated patients with lung contusion.

Oxygen toxicity is considered very rare in any HBOT, especially when most of acute TBI are treated with preventive anti-epileptic drugs. Tension pneumocephalus is another possible rare complication thatcan be avoided by excluding patients with CSF leaks and skull base fractures.

- ***Chronic TBI:***

  Financially: The cost per year ofa patient with PPCS is about $32,000(123). When considering a 40-60 sessions of HBOT, the cost would be$12,000-24,000, which is cost effective by all means even in the first year after treatment. In addition, these numbers do not take into account the loss of work due to PCSand the return to work afterHBOT of those who improve/recover with the treatment.

  Medically: In a recent retrospective analysis, patients suffering from PCS did not have a higher complication rate comparedtoother HBOT patients. The usual risks of 40-60 sessions in HBOT are mild and reversible.

Conclusions:

Acute-subacute TBI:based on the data available today,HBOT may be recommended in acute moderate-severe TBI patients(Type 3 recommendation, level B evidence). Since HBOT reducesmortality, HBOTshould be given as soon as possible(Type 3 recommendation, level B evidence). Myringotomy should be considered in all cases when there is no possibility for self-equilibration of pressure. (Type 3 recommendation, level C evidence). Further studies are needed in order to evaluate the optimal treatment protocol for the different types of injuries(Type 1 recommendation, level A evidence).

Chronic TBI:Based on the data available today,low pressure HBOT(1.5 ATA) may be recommended in chronic TBI (PPCS) for a selected group of patients who have clear evidence of metabolically dysfunctional brain regions(Type 3 recommendation, level B evidence)..

Patients who arecandidates for HBOT should be properly evaluated prior to therapy by standardized cognitive testsand by a functional imaging of the brain(Type 1 recommendation, level B evidence).

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
Tal 2015	Case series	10 patients	Cognitive: Neurotrax computerized tests of memory, attention, executive function, information processing speed including: verbal memory, non-verbal memory, go-no-go test,Stroop, staged information processing test,catch game. Brain imaging: Perfusion MRI	Patients with mTBI for at least 6 months with who have completed two MRI brain imaging	60 min of 100% oxygen at 1.5 ATA X 60 sessions	<u>Outcome post treatment :</u> Significant improvement in the global cognitive scores with a mean change of 6.8±1.9 (p=0.007). The most prominent improvements were seen in information processing speed, visual spatial processing and motor skills indices, with mean changes of 9.6±2.9 (p=0.005), 10.1±4.2 (p=0.0043) and 9.5±4.5 (p=0.013) respectively. significant	Favors the use of HBOT in mTBI Small sample No control group

						increased cerebral blood flow (CBF) and cerebral blood volume (CBV)	
Wolf 2012 (111)	Randomized controlled trial	50 patients	Psychologic: PTSD symptoms – Post traumatic disorder check list –military version (PCL-M) scores Cognition:Immediate post concussion assessment and cognitive testing (ImPACT)	Military servicemembers with at least one combat-related mTBI	HBOT: 90 min of 100% oxygen at 2.4 ATA, 10 minutes air break every 30 minutes X 30 sessions over 8 weeks Sham: 90 min of air(21% Oxygen) at 1.3 ATA X 30 sessions over 8 weeks	Within groups both HBO and Sham groups showed statistically significant improvements in both PCL-M and ImPACT scores over the course of the study (p=0.001). No statistically significant differences between groups were noted, but both groups improved. Concussion history was critical for evaluation	No conclusion due to : Both groups improved more than would be expected greater than 6 months after mTBI. Selection of military service men as patients Secondary gain effect 1.3 ATA as placebo No exclusion of depression, PTSD or other comorbidities
Cifu 2014 (116)	Randomized controlled trial	60 patients (19 and 21 HBOT 21 Sham)	Eye movements in mTBI: saccadic and smooth pursuit parameters	Active Military service with post	Group 1: 60 min of 75% oxygen at 2 ATA X 40	No statistically significant difference	Relocation of patients for a high altitude naval base (NMOTC)

				concussion symptoms for at least 3 months, injury within 3 years, at least 2 months of stable psychiatric status and no chance in psychiatric medications for at least 1 months	sessions over 10 weeks Group 2: 60 min of 100% oxygen at 2 ATA X 40 sessions over 10 weeks Group 3 (Sham): 60 min of 10.5% oxygen at 2 ATA X 40 sessions over 10 weeks	between the groups and no within groups differences (p>0.05 for all measures)	Sham control with hypoxic levels of oxygen Selection of military service men as patients Secondary gain effect 2 ATA as Sham control No exclusion of depression, PTSD or other comorbidities
Cifu 2013(117)	Randomized controlled trial	61 patients (19 and 21 HBOT 21 Sham)	Post concussions symptoms: Rivermeadpost concussion symptom questionnaire (RPQ) Psychological: Post traumatic disorder checklist military version (PCL-M) and centers for epidemiological studies depression scale Cognition: Wechsler adult intelligence	Active Military service with post concussion symptoms for at least 3 months, injury within 3 years, at least 2 months of stable psychiatric status and no chance in psychiatric medications for at least 1	Group 1: 60 min of 75% oxygen at 2 ATA X 40 sessions over 10 weeks Group 2: 60 min of 100% oxygen at 2 ATA X 40 sessions over 10 weeks Group 3 (Sham): 60min of 10.5%	No significant time by intervention interaction was found for any functional, cognitive, or psychomotor secondary outcome. Statistically significant improvement in 2 items of RQP within group 2	No conclusion due to : Relocation of patients for a high altitude naval base (NMOTC) Sham control with hypoxic levels of oxygen Selection of military service men as patients Secondary gain effect 2 ATA as Sham control No exclusion of depression, PTSD or other comorbidities

			scale; Stroop;Trail decision making; continuous performance test; California verbal learning test; paced auditory serial addition test; Benton visual memory test; controlled oral word association test; Grooved peg board. Morbidity: Glasgow outcome scale extended (GOSE) And balance sensory organization test	months	oxygen at 2 ATA X 40 sessions over 10 weeks	($p<0.05$). Other items without significance. Significant decrease in 2 items of PCL-M within group 3 (Sham) ($p=0.03$). Significant decrease in 1 item for group 1 ($p=0.05$). Significant decrease in 2 items as well as the total score in group 3 ($p<0.05$).	
Miller 2015 (118)	Randomized control trial	72 patients (23 Sham, 24 HBO + TBI care, 25 Sham +TBI care)	Post concussions symptoms: Rivermead post-concussion symptoms questionnaire-3 subscale (RPQ-3), Rivermead post-concussion symptoms questionnaire (RPQ), Neurobehaviroal symptom inventory scores (NSI)	Active Military service with at ongoing symptoms with 1 or more mTBI, latest at least within 4 months before randomization, stable medication for 30 days	HBOT: 60 min of 100% oxygen at 1.5 ATA X 40 sessions over 10 weeks Sham: 60 min of 21% oxygen at 1.2 ATA X 40 sessions over 10 weeks	No significant changes between groups in post concussive symptoms and cognition scores. However both groups undergoing supplemental chamber procedures showed	No conclusion due to: Both HBOT and Sham improved more than real placebo group 1.2 ATA HBO as placebo No exclusion of depression, PTSD or other comorbidities Selection of military service men as patients Secondary gain effect

			Cognition: automated neurophyschological assessment metrics (ANAM4 TBI-MIL) Psychological: PTSD checklist – civilian version (PCL-C), center for epidemiologic studies depression scale (CES-D), Beck anxiety inventory (BAI), SF-36 mental health subscale			improvement in symptoms : Within groups, Sham and HBOT groups had significant improvements in post concussion symptoms with ($p<0.04$) while TBI-care group did not improve. Within groups, both HBOT and Sham group had improved neurophysiological scores (p-values not published). PTSD and depression scores tended to favor sham vs. HBOT (p-values not published).	
Boussi-Gross	Randomized controlled trial,	56 patients (32 HBOT,	Cognition: Neurotraxcomputeri	>18 years old patients who	60 minsessions	Significant improvement	Favors the use of HBOT in mTBI

2013 (119)	crossover design	Control/Cross-over 24	zed tests of memory, attention, executive function, information processing speed including: verbal memory, non-verbal memory, go-no-go test,Stroop, staged information processing test,catch game. Quality of life: EQ-5D questionnaire and EQ-VAS Brain functional imaging: SPECT analyzed to calculate the mean perfusion in each broadmann area	suffered mTBI 1-6 years prior to inclusion, at least 1 year of symptoms and no change in cognitive function in the last month	of 100% at 1.5 ATA oxygen X 40 sessions	s were demonstrated in HBOT groups in all cognitive functions: memory ($p<0.0005$), executive function ($p<0.0005$), attention ($p<0.005$) and information processing speed ($p<0.0001$). No significant improvement was observed following the control period ($p>0.2$). Significant improvement in cognitive function in the control group after treatment ($p<0.05$), with no significant difference from the HBOT group ($p>0.4$) Significant	Randomized controlled trial with control group and crossover design Selection of patients with proper functional imaging

						improvement in quality of life in both the HBOT group and the control group after being treated ($p<0.0001$) SPECT imaging revealed elevated brain activity in good agreement with the cognitive improvemens.	
*Churchill 2012(101)	Prospective study	28 patients	Neuropsychological measures, questionnaires, neurologic exams, physical functioning measures	Severe TBI at least 1 year prior to inclusion	60 min of 100% oxygen at 1.5 ATA X 60 sessions	Participants reported improvements in symptoms, such as memory and balance/ coordination. No standardized testing showed clinically important improvement.	No conclusion due to: Small sample size Vague inclusion criteria No control group

Rockswold 2013	Randomized controlled trial	42 patients (22 HBOT, 20 control)	Mortality Morbidity: Glasgow outcome score (GOS) Monitored variables: ICP, Microdyalisate Lactate/Pyruvate and glycerol, PbtO2, CSF F2-Isoprostane, BAL IL-6 and IL-8	Severe TBI (GCS<8) Or Mild-moderate TBI with deterioration to GCS<8 within 48 hours from injury) CT scan grade >I	HBOT/NBH: 60 min of 100% oxygen at 1.5 ATA followed by3 hours 100% oxygen at 1 ATA X 3 sessions Control: standard care	6 months post injury :26% reduced mortality (16% vs 42%, p=0.04) , 36% improvement in favorable outcome (74% vs 38%, p=0.02) Improved cerebral metabolism surrogates Decreased lactate, L/P ratio, ICP and increased PbtO2 within hours after treatment(P< 0.0001)	Favors HBOT use in acute TBI
Bennett 2012 (94)	Meta-analysis	571 patients (285 HBOT, 286 control)	Mortality Morbidity : GOS	Severe TBI	40-60 min of oxygen 100% at 1.5-2.5 ATA X 3-10 sessions	Significant decrease in proportion of unfavorable outcome (P=0.001). Significant decrease in mortality (p=0.003) Number needed to treat to prevent death	Favors HBOT use in acute severe TBI

						=7	
Prakash 2012 (82)	Randomized controlled trial	56 patients – children (28 HBOT, 28 control)	Morbidity: Glasgow coma scale (GCS), disability, duration of hospitalization	Children with severe TBI (GCS<8)	Unknown time and pressure, 3 sessions at 1 week interval, 10-12 days after injury	Outcome at 3 weeks : Improved GCS, decreased duration of hospitalization, decreased disability, improved social behavior (p-values were not published)	Favors the use of HBOT in acute severe TBI Statistics unpublished
Sahni 2012 (100)	Retrospective analysis	40 patients (20 HBOT, 20 control)	Morbidity: Disability rating scale (DRS, Glasgow coma scale (GCS), Ranchos Los Amigos Scale (RLAS)	severe TBI :No clear inclusion criteria – excluded if less than 30 sessions	60 min of 100% oxygen at 1.5 ATA X 30 sessions	Outcome at 1 month post treatment : Decrease in rate of vegetative and extremely vegetative states, decrease in DRS and RLA mean scores. Maximal improvements was seen in the group treated 1-6 months post injury (p-values not published)	Favors the use of HBOT in TBI Statistics unpublished

Harch 2012 (103)	Case series	16 patients	Symptoms: Rivermead PCS questionnaire, neurological exam Psychological: PTSD symptoms by PCL-M, depression by PHQ-9, anxiety by GAD-7 Cognitive: Wechsler adult intelligence scale-IV, WMS memory tests, Stroop test, TOVA impulsivity, TOVA variability, grooved pegboard Quality of life: MPQoL, self report Brain imaging : SPECT	18-65 years old retired/active military service , with post concussion symptoms due to mild-moderate TBI due to blast injury at least 1 year prior to inclusion	60 min of 100% oxygen at 1.5 ATA X 40 sessions	80% reported on improved symptoms 100% had improved physical examination Significant improvement in cognitive functions IQ ($p<0.001$), working memory ($p=0.003$), Stroop test ($p<0.001$), memory ($p=0.02$), TOVA impulsivity ($p=0.04$). Significant improvement in psychological scores : PTSD ($p<0.001$), Rivermead PCSQ ($p=0.0002$), anxiety ($p=0.007$), depression ($p<0.001$)	No conclusion due to : No control group Small sample Size Secondary gain of military subjects Rivermead PCS score

						Improved quality of life (p=0.003) Significant increases in mean perfusion in white matter and some gray matter ROIs	
Lee 2012 (110)	Case report	1 patient	none	15 months post severe TBI	unknown	Rare complication: tension pneumocephalus	Case report: patients with unrepaired skull base fracture and cerebrospinal fluid diversion be carefully evaluated before receiving hyperbaric oxygen therapy
Lv LQ 2011 (104)	Case series	6 patients	Paroxysmal sympathetic hyperactivity (PSH)	Paroxysmal sympathetic hyperactivity following extremely severe TBI	Non-published	Improved control of PSH changes (no statistics), after failure of standard care	No conclusion due to : Case report Small sample No control group
Rockswold 2010 (86)	Randomized controlled trial	69 patients: 26 HBO + standard care, 21 normobarichy peroxia + standard care, 22 standard care	Brain tissue PO(2), microdialysis, and intracranial pressure Cerebral blood flow (CBF), arteriovenous differences in oxygen, cerebral metabolic rate of oxygen (CMRO2), CSF lactate and F2-isoprostane	Severe TBI (GCS<9)	90 min of 100% oxygen at 1.5 ATA X 3 sessions	Outcome within hours : ICP was significantly lower statistically after HBO2 until the next treatment session ($p < 0.001$) in comparison with levels in the control	Favors the physiological effect of HBO in acute TBI

			concentrations, and bronchial alveolar lavage (BAL) fluid interleukin (IL)-8 and IL-6			group Brain tissue PO2 levels were significantly increased in HBOT group and remained high until the next treatment session (p =0.003). HBOT significantly increased CBF and CMRO2 for 6 hours (p < or = 0.01). Microdialysis lactate/pyruvate (L/P) ratios were significantly decreased post-treatment HBOT group (p < 0.05)	
Mao 2010 (90)	Randomized controlled trial	60 patients (30 HBOT +standard treatment, 30 standard	Morbidity: GCS, GOS EEG changes	Severe TBI (GCS<8) within 24 hours of injury	Unknown protocol, started 12 days post injury	Outcome at 3 months post treatment : GCS at 20 d,30 d,90 d	Favors the use in acute TBI GCS as continuous parameters

		treatment)				post treatment in HBO group were significantly increased (P=0. 05) score of GOS in HBO group was significantly higher than in control group (P=0. 01) Compared with control group,the scores of EEG at 30 d,90 d post treatment in HBO group were significantly decreased	
Wright 2009 (105)	Case report	2 patients	PCS symptoms Cognitive: Automated neuropsychological assessment metrics (ANAM)	Military service men with PCS induced by blast injury 6 months after injury	60 min of 100% oxygen at 1.5 ATA X unknown number of sessions	Improved symptoms (headaches and sleep) improved ANAM scores in all domains up to normalization of scores to pre-injury	Case report Small sample No control

						levels	
Harch 2009 (107)	Case report	1 patient	PCS symptoms PTSD symptoms, Brain imaging: SPECT	Military veteran with PCS and PTSD induced by blast injury 3 years earlier	60 min of 100% oxygen at 1.5 ATA for X 39 sessions	improvement in his post-concussive symptoms and PTSD symptoms improvements in brain blood flow at bilateral frontal and temporal defects	Case report Small sample
Lee 2009(84)	Case report	1 patient	None	Acute severe TBI	unknown	Rare complication of tension pneumocephalus	Case report : Pneumocephalus, untreated skull base fracture, and CSF leakage may be considered contraindications to HBOT
Lin JW 2008 (91)	Randomized controlled trial	44 patients (22 HBOT, 22 control)	Morbidity: Glasgow coma scale (GCS), Glasgow outcome scale (GOS)	Moderate-severe subacute TBI, treated after an average of 22-32 days from injury	90 min of 100% oxygen at 2 ATA X 20 sessions	Outcome at 6 months post HBOT : HBO2 group achieved statistically significant better GCS scores than the control group post-intervention ($p<0.05$) No significant differnces between groups	Favors HBO for subacute TBI No analysis per severity GCS as continuous parameter

						stratified to GOS 2-3 at 3 & 6months Statistically significant improvement between HBO group versus control in group stratified to GOS=4 at baseline ($p<0.05$)	
Xie 2007 (92)	Randomized controlled trial	60 patients (30 HBOT + neurosurgical care, 30 neurosurgical care)	Morbidity: Glasgow coma scale (GCS) C-Reactive-Protein	Acute TBI within the last 24 hours prior to inclusion GCS 3-12	80 min of 100% oxygen at 2-2.5 ATA X2-10 sessions	Post treatment : There was a statistically significant difference between HBO2 group and control group after treatment ($P < 0.01$).	Favors the use of HBO in acute TBI GCS as continuous parameters No analysis per severity
Hardy 2007 (108)	Case report	1 patient	EEG, metabolic and behavioral measurements	TBI 1 year prior 8to inclusion	60 min of 100% oxygen at 2 ATA for 20 sessions, and another 60 sessions 1 year later	Improvements in sensorimotor functions and neuropsychological improvements There was an enhanced P300 amplitude in the damaged	Case report

						hemisphere. Gains were no longer observed one year after treatment. However, after an additional treatment series of 60 exposures, the improvements were reinstated	
Shi XY 2006 (102)	Prospective study	310 patients	Brain imaging: SPECT, CT	History of trauma at least 1 month prior to inclusion and had PCS symptoms or epilepsy	90 minutes of 96% oxygen at 2 ATA X 20 sessions	Normalization of brain perfusion by 50% (from 81.3% to 29.7% abnormal areas). Improved symptoms (unknown proportion)	No conclusion due to : No control group Unknown clinical value
Golden Z 2006 (120)	Prospective study	63 patients (42 HBOT, 21 control)	Cognitive: Stroop, Luria-Nebraska neuropsychological battery, word fluency, logical memory	Chronic brain injury for at least 2 years	unknown	Significant gains in all neuropsychological areas compared to the control ($p<0.0001$)	Favors the use of HBOT in brain injury Unknown chronic brain injury source Unknown HBOT protocol Nonrandomized controlled
Barrett KF 2004(106)	Nonrandomized prospective	5 HBOT, 5 head injury controls, 5	Cognitive: memory, mental tracking, attention,	TBI at least 3 years from injury	60 min of 100% oxygen at at	No consistent change was seen in the	No conclusion due to small sample

		normal controls, 68 normal controls for SPECT controls	concentration, executive function, affect, motor. Specific tests: adaptive rate continuous performance, Wisconsin card sorting test, nonverbal intelligence-2, controlled oral word association, verbal selective reminding test, digit span. Behavioral: geriatric depression scale Symptoms: progressive exercise test Brain imaging: MRI, SPECT		1.5 ATA X 80 sessions + another 40sessions after 5 months break	neuropsycho metric scores No consistent patterns of perfusion changes over time in SPECT Global depression scores were stable	
Mitani 2004 (83)	Case series	Unknown	Morbidity: Glasgow coma scale (GCS)	Acute severe TBI	Unknown	Outcome post treatment : Improvements were observed in some acute subdural hematoma patients, yet the overall outcome was poor. Mild to	

						moderate diffuse axonal injury patients recovered well. Poor outcomes in severe diffuse axonal injury	
Shi XY 2003 (121)	Randomized controlled trial	320 patients (195 HBO + medication, 125 medication only)	Symptoms Brain imaging: SPECT	Unknown	90 min of 96% oxygen at 2 ATA X 20-40 sessions	Significant difference in recovery of clinical symptoms, control of epilepsy, and resolution of hydrocephalus (P<0.01).	Favors the use of HBO in TBI Unknown inclusion criteria
Ren H 2001 (88)	Randomized controlled trial	55 patients (35 HBOT + standard care, 20 standard care)	Morbidity: Glasgow coma scale (GCS), Glasgow outcome scale (GOS) Brain imaging:electric activity mapping (BEAM)	Severe TBI (GCS<8)	40-60 min of 100% oxygen at 2.5 ATA X 30-40 sessions	Outcome at 6 months post treatment : HBO2 group showed statistically significant improvement over control group (p<0.01) HBO2 group showed statistically significant improvement over control	Favors HBO for acute TBI

						group at 6 months after injury (p<0.001)	
Woolley SM 1999 (109)	Case report	1 patient	Postural stability and walking	Severe TBI 2 years prior to study	60 min of 100% oxygen at 1.5 ATA, bi-daily X 40 sessions	Mild improvement immediately post treatment, This improvement was not evdient 6 weeks later	Disfavors the use of HBO in TBI : Case report
Neubauer RA 1994	Case report	1 patient	Motor evaluation, cognitive evaluation SPECT	Severe TBI 1 year prior to study	Unknown time of 100% oxygen at1.5-1.75 ATA X 188 sessions	Improved motor and cognitive functions, normalized SPECT areas	Favors the use of HBO in TBI : Case report
Rockswold 1992 (85)	Randomized controlled trial	168 patients(84 HBOT +standard care, 82 standard care)	Mortality Morbidity: Glasgow coma scale (GCS), Glasgow outcome scale (GCS) Intracerebral pressure (ICP)	Severe TBI with GCS <10 for at least 6 hours	60 min of 100% oxygen at 1.5 ATA, three time daily average of 21 sessions	Outcome at 1.5 year : Mortality rate decreased to 17% compared to 32% in the control group (p = 0.037). Mortality in patients with an initial GCS score of 4-6 decreased to 17% compared to 42% in the control group	Favors the use of HBO in acute TBI

						(p=0.04) Mortality in patients with high ICP (>20mmHg) decreased to 21% compared to 48% in the control group (p=0.02)	
Artru 1976 (93)	Randomized controlled trial	60 patients (31 HBOT, 29 standard care)	Mortality Morbidity: Glasgow outcome scale (GOS)	Severe TBI with COMA	60 min of 100% oxygen at 2.5 ATA X 10 daily sessions, followed by 4 days rest and repeat if not responding	Outcome at 1 year: In a subgroup of young patients with brainstem injury, HBO2 group had statistically significant higher rates of recovered consciousness at 1 month (p<0.03)	Favors HBO use in some cases of acute TBI HBOT protocol was intermittent and inconsistent
Mogami 1969 (95)	Prospective study	66 patients (51 TBI)	Symptoms EEG Cerebrospinal fluid pressure Lactate/Pyruvate levels	Severe acute cerebral damage	60 min of 100% oxygen 2 ATA + 6 sessions in 3 ATA	Outcome post treatment : Temporary neurological improvements were observed in 50% of the patients. 33% had remarkable degree of	Favors the use of HBO in acute TBI No control group No statistical analysis

						clinical improvement which included restoration of mental and neurological function reduction of EEG abnormalities was noted in 33% of the patients.	

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