Policy Issue: Traumatic brain injury (TBI) and post traumatic stress disorder (PTSD) are signature injuries among Veterans of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF). Hyperbaric oxygen (HBO2) has been used to treat certain injuries (e.g., dive-related injuries, soft tissue injuries, carbon monoxide poisoning). Recently, it has been proposed as treatment for individuals with TBI or PTSD.

In August 2009, increasing interest in HBO2 for treatment of TBI prompted the Principle Deputy Under Secretary for Health to request a review by the Technology Assessment Advisory Group (TAAG) within the VA Office of Patient Care Services. The TAAG provides unbiased, evidence-based advice and recommendations for new healthcare technologies used in VA. The TAAG considers input from several sources such as the VA Technology Assessment Program (TAP), Clinical Expert Panels (CEPs) and a Utilization and Cost Analysis (UCA).

In January 2010, the Secretary of Veterans Affairs requested an updated review of the research on HBO2 for treatment of PTSD to support definitive VA policy. The purpose of this report is to provide the TAAG with a catalogue of published, peer-reviewed evidence on the appropriate clinical use of HBO2 for the Veteran population for treatment of TBI or PTSD.

Regulation and reimbursement: The US Food and Drug Administration (FDA) classifies a hyperbaric chamber as a prescriptive Class 2 device that is intended to increase the environmental oxygen pressure to promote the movement of oxygen from the environment to a patient's tissue by means of pressurization that is greater than atmospheric pressure; this device does not include topical oxygen chambers for extremities (21CFR878.5650). Manufacturers of hyperbaric chambers are required to submit a Premarket Notification [510(k)] verifying the safety of the device and its intended prescribed uses. FDA requires investigational new drug (IND) registration of HBO2 for research purposes. FDA categorizes HBO2 as “more than minimal risk”; there is a 1:3000 risk of provoked seizures and small risk of fire/explosion.

FDA-approved indications are listed in Table 1. Historically, these indications have been adopted from the Hyperbaric Oxygen Therapy Committee Report produced by the Undersea & Hyperbaric Medical Society.¹

The US Department of Health and Human Services Centers for Medicare and Medicaid Services (CMS) limits reimbursement for HBO2 therapy to that which is administered in a chamber (including the one man unit) for the indications listed in Table 1.² CMS does not authorize HBO2 as standard of care for TBI or PTSD, nor is it a reimbursable benefit for civilian providers by other third party payers.³


www.va.gov/vatap

January 2010
Table 1. Regulation and reimbursement of HBO2

<table>
<thead>
<tr>
<th>Indication</th>
<th>FDA-approved</th>
<th>CMS Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air or Gas Embolism</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Carbon Monoxide Poisoning or Carbon Monoxide Poisoning Complicated by Cyanide Poisoning</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clostridial Myositis and Myonecrosis (Gas Gangrene)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Crush Injury, Compartment Syndrome, and other Acute Traumatic Ischemias</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Decompression Sickness</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Enhancement of Healing in Selected Problem Wounds</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Exceptional Blood Loss (Anemia)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Intracranial Abscess</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Necrotizing Soft Tissue Infections</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Osteomyelitis (Refractory)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Delayed Radiation Injury (Soft Tissue and Bony Necrosis)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Skin Grafts &amp; Flaps (Compromised)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Thermal Burns</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Diabetic wounds of the lower extremities (Refractory)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Actinomycosis (Refractory)</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Methods: To meet the client’s urgent information needs, TAP sought the results of existing systematic reviews and health technology assessments (HTA) and supplemented them with updated searches of published primary data. In the case of TBI, results were confined to controlled clinical trials; in the case of PTSD, being a new indication for use, all research data were included.

On August 12, 2009, TAP searched Medline, Embase and Current Contents using the Dialog Information Service, the HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA; www.inahta.org), and the Cochrane Library using search terms for hyperbaric oxygen crossed with search terms for brain or head injury, concussion, trauma or for military related citations. TAP applied an evidence filter to identify high quality publications types such as meta-analyses, systematic reviews, and evidence-based guidelines or recommendations published in English and which synthesize research with adult human subjects. TAP conducted a second search for controlled trials published subsequent to when the available systematic reviews had concluded their searches. On August 18, 2009 TAP queried members of the International Network of Agencies for HTA (INAHTA; www.inahta.org) through its electronic listserv for existing reports or reports in progress that were not listed in existing electronic databases. These results are presented in Table 4.

On January 25, 2010 TAP updated searches for TBI using the above strategy and retrieved seven additional citations. TAP expanded its searches to include indications for PTSD (See Appendix). After first searching The Cochrane Library with no results, searches were done in 13 biomedical/health /life sciences/clinical databases available through the Dialog Information Service.
Service. They were searched very broadly using a comprehensive list of terms indicating PTSD and were then combined with a list of hyperbaric oxygen treatment terms. Ultimately, this search retrieved 96 unique citations. TAP initiated another INAHTA query on January 25, 2010 for updated information regarding HBO2 treatment for either TBI or PTSD.

Results: Searches, review of end references of retrieved systematic reviews and responses from INAHTA members captured 220 citations, of which 43 were retrieved as potentially relevant to the report. An overview of the search results confirm a substantial body of research on the clinical uses of HBO2 as evidenced by the growing number of organizations involved in conducting health technology assessments (HTA) and systematic reviews on the subject.

HTAs and systematic reviews of HBO2 for TBI have emerged in recent years as the body of clinical research increases for this indication (See Tables 2 and 4). In addition to these reviews, results from one newly published controlled clinical trial was identified (Rockswold 2009).

For PTSD, no systematic reviews or HTAs were identified, and only one case report was identified reporting on the use of HBO2 in a young military Veteran with post-concussion syndrome and PTSD (Harch 2009; see end reference for abstract).

Ongoing clinical research is presented in Table 3.

Table 2. Summary of systematic reviews of HBO2 for TBI

<table>
<thead>
<tr>
<th>Citation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritchie 2008</td>
<td>• Some evidence of reduced risk of death from TBI but little evidence of better functional outcome among survivors (based on Bennett 2004 and McDonagh 2004 and five new observational studies)</td>
</tr>
<tr>
<td></td>
<td>• Adverse effects were poorly assessed</td>
</tr>
<tr>
<td>De Laet 2008</td>
<td>Very low quality evidence from small trials for a reduced risk of death, without evidence for improved outcomes in terms of quality of life (includes Bennett 2004)</td>
</tr>
<tr>
<td>Pichon-Riviere 2006</td>
<td>• Insufficient evidence (based on Bennett 2004)</td>
</tr>
<tr>
<td></td>
<td>• Not recommended for clinical use</td>
</tr>
<tr>
<td>Bennett 2004</td>
<td>Limited evidence of reduced mortality or that survivors have improved quality of life</td>
</tr>
<tr>
<td>(Cochrane review)</td>
<td></td>
</tr>
<tr>
<td>McDonagh 2003</td>
<td>• Conflicting and inconclusive evidence of effectiveness</td>
</tr>
<tr>
<td>(for AHRQ)</td>
<td>• Potential small mortality benefit which may depend on subgroup selection</td>
</tr>
<tr>
<td></td>
<td>• Effect on functional status and incidence and clinical significance of adverse effects are unclear</td>
</tr>
<tr>
<td>Oppel 2003</td>
<td>• Strongest evidence indicated either no effect or harm from HBO2 use</td>
</tr>
<tr>
<td></td>
<td>• Use of HBO2 not supported</td>
</tr>
<tr>
<td>Avalia-t 2003</td>
<td>• Insufficient evidence (in Spanish)</td>
</tr>
</tbody>
</table>

Conclusions: Traumatic brain injury. The systematic reviews by McDonagh (2003) and Bennett (2004) provide the most rigorous and current information on the status of the clinical research for the use of HBO2 in TBI. Subsequent reviews identified these two reviews as the primary basis for their conclusions. To summarize their results, the clinical value of HBO2 in treating TBI is unknown due to insufficient evidence proving its effectiveness or ineffectiveness. Several case reports suggest positive outcomes for patients with TBI, but these studies were inconclusive for determining effectiveness as they were not randomized, controlled, or blinded.
studies. Therefore, it is unknown whether individual case reports of recovery are due directly to HBO2 therapeutic benefit, or natural recovery of each individual. The degree to which placebo effect may account for both symptom and imaging improvement in delayed treatment reports remains unknown. Promising results from animal studies have not as yet translated to humans. High quality research is needed to determine clinical efficacy of HBO2 in TBI treatment.

TAP’s updated searches uncovered one recently published Phase II trial (See Table 3 below; NCT00170352). This study assessed evaluated the use of HBO2 and 100% FiO2 (fraction of inspired oxygen delivered) separately and in combination compared with standard care in a cohort of ventilated subjects with an acute severe TBI (GCS score ≤ 8) within 24 hours of injury. Subjects received hyperoxia treatments every 24 hours for three treatment sessions. HBO2 delivered to achieve a brain tissue P02 > 200 mm Hg has a greater positive effect than normobaric hyperoxia therapy on oxidative cerebral metabolism and intracranial pressure. Effect was sustained for at least six hours post treatment over the course of three treatment sessions without pulmonary or cerebral oxygen toxicity. Results suggest hyperoxia treatment in subjects with early, severe TBI may be safe and efficacious, and several clinical trials are in progress that may help inform these results (see Table 3). However, improvement in mortality or morbidity over the long-term requires further study.

Conclusions: Post traumatic stress disorder. As only one case report was identified, the threshold for rigorous evidence of effectiveness for the treatment of PTSD with HBO2 has not been met. Existing evidence in the published research and popular press comprises anecdotes of promise and potential for this technology at times by proponents of HBO2 with financial and professional interests. Unbiased, independent research assessing the safety, feasibility and relative effectiveness of HBO2 is needed especially in a cohort of Veterans whose treatment options may otherwise be limited.

Ongoing research:


<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
<th>Title</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00170352</td>
<td>Comparison Between Different Types of Oxygen Treatment Following Traumatic Brain Injury</td>
<td>II</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT00594503</td>
<td>Hyperbaric Oxygen Therapy and SPECT Brain Imaging in Traumatic Brain Injury</td>
<td>I</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT00715052</td>
<td>The Effect of Hyperbaric Oxygen Therapy on Patients Suffering From Neurologic Deficiency Due Traumatic Brain Injury</td>
<td>Not reported</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT00760734</td>
<td>Pilot Study of Hyperbaric Oxygen Therapy (HBOT) in Chronic Traumatic Brain Injury (TBI)/Post Concussion Syndrome (PCS) and TBI/Post-Traumatic Stress Disorder (PTSD)</td>
<td>I</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT00810615</td>
<td>Treatment of Traumatic Brain Injury With Hyperbaric Oxygen</td>
<td>I / II</td>
<td>Enrolling by invitation</td>
</tr>
<tr>
<td>NCT00830453</td>
<td>Hyperbaric Oxygen Therapy in Chronic Stable Brain Injury (HYBOBI)</td>
<td>II</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

VA and Department of Defense (DoD) are collaborating to improve the knowledge and use of HBOT in TBI. In 2008, the U.S. Navy Surgeon General convened a Steering Group of experts
from VA, DoD and academia, and tasked the Defense Center of Excellence (DCoE) for Psychological Health and TBI to lead efforts in determining the current scientific status of HBO2 in TBI. The Steering Group completed a comprehensive review of medical literature and convened a consensus conference in December 2008. They reviewed basic neuroscience of mild TBI/concussion, anecdotal reports of use, pilot studies and possible outcome measures.

The Steering Group concluded the following:

- At present, HBO2 cannot be accepted as standard-of-care for Service Members or Veterans with TBI.
- Exceptions to provide HBO2 for patients with TBI are currently offered on a limited case by case basis.
- HBO2 case reports are compelling enough to mandate expedited research trials.
- DoD and VA should conduct focused, expedited research of HBO2 in chronic, mild TBI via rigorous clinical trials to determine benefit.

From the consensus conference the Steering Group developed a research protocol from which DCoE is expediting a DoD-funded prospective clinical trial at four DoD facilities to investigate the efficacy of HBO2 for symptomatic, chronic mild and moderate TBI, with and without PTSD. This large, randomized, double-blinded, controlled multi-center study will be powered to be a definitive study (Phase 3) determining efficacy of HBO2 in chronic, mild and moderate TBI. Full study completion and outcome assessment of the entire cohort is projected by December 2010. A Data Safety Monitoring Board will begin to review preliminary results of data in the fall of 2009.

In addition, two Phase 2 DoD/VA studies are planned or underway:

1. In January 2009, the Defense Advanced Research Projects Agency (DARPA) and the Telemedicine & Advanced Technology Research Center (TATRC) funded the Richmond VA Medical Center and Virginia Commonwealth University to perform a feasibility study: “Hyperbaric Oxygen Therapy for Post-Concussive Symptoms after mild Traumatic Brain Injury: A Randomized, Double-Blinded, Sham-Controlled, Variable Dose, Prospective Trial” (Dr. David Cifu, Principle Investigator, Richmond VAMC). The study will be in partnership with the Naval Operational Medicine Institute in Pensacola, FL and Quantico Marine Corp base (status: in planning stage).

2. An Air Force-sponsored double-blind pilot study (50 patients) began at Wilford Hall Medical Center in San Antonio, TX in February 2009 for use of HBO2 for mild TBI symptoms (See Table 3; NCT00810615). The study will provide safety and feasibility data regarding dose level. Results of this study are anticipated April 2010.

4 Contact for Further Information: Dr. David Chandler, VHA Deputy Chief Consultant Rehabilitation Service (117) Tel: (202) 461-7353; e-mail: david.chandler2@va.gov.
Table 4. Relevant responses from INAHTA members of evaluations of HBO2 for TBI or PTSD

<table>
<thead>
<tr>
<th>Agency</th>
<th>Response</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICTAHC (Israel)</td>
<td>The Effect of Hyperbaric Oxygen Therapy on Patients Suffering From Neurologic Deficiency Due Traumatic Brain Injury. Zerifin, Israel. ClinicalTrials.gov identifier: NCT00715052. (actively recruiting; estimated completion Jan 2010). The aim of the RCT is to evaluate the effect of HBO2 on patients with chronic neurologic deficiency due to TBI using clinical/cognitive tests and functional brain imaging with SPECT. Encouraging interim results reported by principal investigator but no data available</td>
<td></td>
</tr>
<tr>
<td>IHE (Canada)</td>
<td>Report provided: Hyperbaric oxygen therapy – recent findings on evidence for its effectiveness published in 2003 by the Alberta Heritage Foundation for Medical Research. This report can also be accessed from the Institute of Health Economics website at: <a href="http://www.ihe.ca/documents/hyperbaric_oxygen_therapy.pdf">Link</a> PTSD not covered TBI—inconclusive</td>
<td></td>
</tr>
</tbody>
</table>
### Agency | Response | Findings
--- | --- | ---
**NHSQIS** (Scotland) | Reports 74C (D/2008/10.273/15). Refer to section 3.4.16 'miscellaneous indications' for TBI. In part 3.4.9 evidence for the indication 'Post-anoxic encephalopathy' is also discussed. In English. Citation forwarded to VATAP: Bennett MH, Trytko B, Jonker B. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database of Systematic Reviews: Reviews 2004 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004609.pub2. 2004(4). | TBI—inconclusive PTSD not covered


**ZonMW** (The Neth.) | Guidelines for the use of HBOT have been published by The Swedish society of anaesthesia and intensive care ([www.sfai.se](http://www.sfai.se)). HBOT is not used for treating traumatic brain injury. | Not used

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SBU
Possibly no clinical trials funded at this time. Another possible contact is the Institute of Hyperbaric Medicine in Holland, their site is: [http://www.ivhg.nl/startpaginaansti.html](http://www.ivhg.nl/startpaginaansti.html) Three locations are involved: info-rotterdam@ivhg.nl info@ivhg.nl info-arnhem@ivhg.nl
APPENDIX

Dialog Information Services – Search strategy for PTSD and HBO2 – January 25, 2010
13 Databases Searched:
1. MEDLINE
2. EMBASE
3. Current Contents
4. PsycINFO
5. BIOSIS
6. CSA – Life Sciences
7. SCI-Search
8. Social SCI-Search
9. Global Health
10. Federal Research in Progress
11. Gale Group Health & Wellness
12. General Science Abstracts
13. NewsRx Weekly Reports

S STRESS DISORDERS, POST-TRAUMATIC?/DE OR POSTTRAUMATIC STRESS DISORDER?/DE
S PTSD/TI,AB,GS,KW,SH

S COMBAT(2N)NEURS?/TI,DE OR COMBAT(2N)DISORDER?/TI,DE OR
COMBAT(2N)FATIGUE?/TI,DE OR COMBAT(2N)PSYCHO?/TI,DE OR COMBAT(2N)PSYCHI?/TI,DE

S (POSTTRAUMATIC? OR POST()TRAUMATIC?)/TI,DE(1N)(STRESS? OR NEUROS? OR
DISORDER? OR PSYCHIATR? OR PSYCHO? OR PSYCHIC?)/TI,DE

S (WAR()TIME OR WARTIME OR COMBAT OR OIF OR OEF OR WAR OR TORTUR??? ? OR
OUTCOME? OR SEQUEL? OR
AFTER()EFFECT? OR MENTAL()HEALTH OR MENTAL? OR PSYCHOSOCIAL? OR
PSYCHO()SOCIAL? OR INTRUSIVE()MEMOR?)/TI,DE

S (WAR? ? OR TERROR? OR OIF OR OEF OR COMBAT OR IRAQ OR AFGHAN? OR DEPLOY? OR
RE()DEPLOY?)/TI,DE

S S1 OR S2 OR S3 OR S4 OR S5 OR S6
S NOT HUMAN? ?/DE,GS

RESULTS COMBINED WITH HYPERBARIC TERMS –

S HYPERBARIC?(N)OXYGEN?/TI,DE
S OXYGEN?(N)HYPERBARIC/TI,DE OR HIGH()TENSION? OR PRESSUR?()OXYGEN?/TI
S HYPERBARIC?(N)REOXYGEN?/TI,DE

YIELDING - 95 unique citations, of these 1 case report directly relevant.
END REFERENCES


Avalia-t. Indicaciones de la oxigenoterapia hiperbárica. SERIE CONSULTAS TÉCNICAS CT Santiago de Compostela. Axencia de Avaliación de Tecnoloxías Sanitarias (avalia-t), 2003:(8). (In Spanish.)


Harch PG, Fogarty EF, Staab PK, Van Meter K. Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post traumatic stress disorder: a case report. Cases Journal, 2009; 2: 6538. A 25-year-old male military veteran presented with diagnoses of post concussion syndrome and post traumatic stress disorder three years after loss of consciousness from an explosion in combat. The patient underwent single photon emission computed tomography brain blood flow imaging before and after a block of thirty-nine 1.5 atmospheres absolute hyperbaric oxygen treatments. The patient experienced a permanent marked improvement in his post-concussive symptoms, physical exam findings, and brain blood flow. In addition, he experienced a complete resolution of post-traumatic stress disorder symptoms. After treatment he became and has remained employed for eight consecutive months. This case suggests a novel treatment for the combined diagnoses of blast-induced post-concussion syndrome and post-traumatic stress disorder.


Policy Issue: Traumatic brain injury (TBI) is frequent injury among veterans of Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND). Stroke is a serious health issue for Veterans and the entire U.S. adult population. Hyperbaric oxygen (HBO2) is effective in treating certain injuries (e.g., dive-related injuries, soft tissue injuries, carbon monoxide poisoning). In January, 2010, the role of HBO2 in treating Veterans with TBI and other forms of brain injury was considered by a Clinical Review Team in Patient Care Services (PCS). The 2010 PCS report concluded the following:

- At present, HBO2 cannot be accepted as standard-of-care for Service Members or Veterans with TBI.
- Exceptions to provide HBO2 for patients with TBI are currently offered on a limited case by case basis.
- HBO2 case reports are compelling enough to mandate expedited research trials.
- DoD and VA should conduct focused, expedited research of HBO2 in chronic, mild TBI via rigorous clinical trials to determine benefit.

Based upon two clinical studies performed in Israel that suggested that HBO2 could be useful for treating adults who had suffered stroke [1] or TBI,[2] the Secretary of the Department of Veterans Affairs requested an updated evaluation of the value of HBO2 for treating Veterans with TBI or stroke. Dr. M. Agarwal assigned two members of the 2010 group that reviewed HBO2 to report on the current utility of HBO2 for treating Veterans with stroke or TBI. Dr. R.L. Ruff, is the National Director for Neurology in VHA and Dr. D.X. Cifu is the National Director for Rehabilitation Medicine and the Polytrauma System of Care in VHA.

This report includes a catalogue of articles published between 01/01/2010 and 01/17/2014 in peer-reviewed journals on the appropriate clinical use of HBO2 for the veteran population for treatment of TBI and stroke as an Appendix.

Regulation and reimbursement: The US Food and Drug Administration (FDA) continues to classify a hyperbaric chamber as a prescriptive Class 2 device that is intended to increase the environmental oxygen pressure to promote the movement of oxygen from the environment to a patient's tissue by means of pressurization that is greater than atmospheric pressure; this device does not include topical oxygen chambers for extremities (21CFR878.5650). The information that is relevant for this section has not changed since the 2010 report. The US Department of Health and Human Services Centers for Medicare and Medicaid Services (CMS) does not authorize HBO2 as standard of care for TBI or stroke, nor is it a reimbursable benefit for civilian providers by third party payers.

Methods: Dr. Ruff reviewed the medical literature from January 1, 2010 through January 18, 2014 for all clinical studies involving HBO2 and TBI and in the case of stroke because there were few clinical studies, all studies involving HBO2 were considered. The literature search was performed on January 18, 2014 by querying the Medline, Embase and Current Contents using the Dialog Information Service, the HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA; www.inahta.org), and the Cochrane Library using search terms for hyperbaric oxygen crossed with traumatic brain injury or stroke.
Results: Searches, review of end references of retrieved systematic reviews and responses captured 76 citations. All of the citations were reviewed and 22 were relevant to this report. The appendix contains the relevant references including the article abstracts where available. An overview of the search results confirm a substantial body of research on the clinical uses of HBO2 as evidenced by the growing number of organizations involved in conducting health technology assessments (HTA) and systematic reviews on the subject. However, the cumulative findings of the studies indicate that there is insufficient support for using HBO2 to treat Veterans for residual deficits following stroke or for sequelae of combat or other TBI. The newest publications on cooperative studies conducted by the VA and Department of Defense (DoD) provide clear direct Veteran-centric evidence that HBO2 does not improve the outcome following combat TBI. The following text summarizes the studies of HBO2 for TBI and stroke.

HBO2 treatment for TBI: There were 10 papers reporting the findings of clinical trials of HBO2 for treating TBI.[2-11] The 5 papers that were most relevant for the VHA described VA/DoD cooperative clinical trials of HBO2 for combat TBI.[3-7] These reports were published in 2014,[3] 2013 [4, 5] and 2012.[6, 7] The subjects sustained TBI in combat in Iraq or Afghanistan. The VA/DoD studies were carefully constructed, controlled, blinded studies that were the only studies to incorporate valid sham-treatment study groups. The findings of the VA/DoD studies were clear and unequivocal HBO2 treatment did not improve the outcome of any group of military personnel who had any level of severity of combat TBI. An Israeli clinical study of HBO2 for people with long-term sequelae of mild TBI [2] reported improvement in cognitive performance and self-perceived quality of life. In addition the study reported differences in patterns of metabolic activity determined using single photon emission computerized tomography (SPECT). The severest limitations of this single study compared with the 5 VA/DoD are: 1) the study did not incorporate a valid sham-treated control group, 2) the subjects and examiners were not effectively blinded about HBO2 treatment and 3) the outcome measures were susceptible to improving based upon the subjects expectation as to whether they should improve or not. The last criticism could explain many of the reported improvements in cognitive performance. The 5 VA/DoD reports [3-7] are more relevant to VHA because the studies were better designed and were Veteran-centric clinical trials.

There were 4 other reports of clinical trials of HBO2 for civilian TBI populations.[8-11] Two of the studies were reported in 2013, [8, 9] and incorporated valid HBO2 control groups. One study evaluated HBO2 for treatment of subjects with severe TBI [8] the other study evaluated subjects with chronic manifestations of TBI [9]. These two controlled studies reported no clinical benefits from HBO2 treatment.[8, 9] Two other studies reported in 2012 [10] and 2010 [11] reported no improvements on measures of clinical outcomes. One of these studies noted that subjects reported subjective changes associated with HBO2 treatment, but the subjects in this study were not blinded and may have reported feeling differently because they expected to improve.[11] Consequently, for these 4 studies of HBO2 in civilian study groups, there were no improvements in objective clinical measures due to HBO2 treatment.[8-10]

There were two studies that emphasized serious side effects from HBO2 treatment.[12, 13] One study raised concern about accumulation of air in the brain (tension pneumocephalus) resulting from HBO2.[13] Consequently, HBO2 is not benign.

A Cochrane review of clinical studies of HBO2 for TBI considered clinical studies reported through March, 2012.[14] This report concluded that there was no data from blinded controlled clinical studies that demonstrated efficacy for HBO2 as a treatment for TBI. The design of the Israeli study that reported benefit from HBO2 for people with persisting manifestations of concussion, [2] was not adequately blinded or controlled according to the
criteria presented in this Cochrane review.[14] In contrast the VA/DoD studies that evaluated HBO2 for combat TBI [3-7] were well designed and executed and these studies met the design criteria set forth in the Cochrane review.[14]

**HBO2 treatment for stroke:** The rationale for HBO2 improving the function of people who survived a stroke is that the stroke-injured brain has populations of neurons that are alive, but not fully functional due to not receiving enough blood. The area of brain tissue with inadequate blood flow is referred to as the “ischemic penumbra.”[10] There are theoretic and practical problems with the concepts of an ischemic penumbra. Neurons have a very sharp plateau for death when blood flow drops below the critical level needed for survival. Pathological studies of the brains of stroke victims demonstrated that the transition zone between normal brain tissue and brain that was dead due to loss of blood flow was extremely narrow, less than 0.1 mm. Consequently, the ischemic penumbra, if it exists, is small. There are several problems with the concept of using increased partial pressure of oxygen to improve the function of neurons that do not receive enough blood flow. The first is that reduction in blood flow damages neurons due to deficiency of glucose as well as do to deficiency of oxygen. Increasing the oxygen availability does not address the lack of glucose. A second problem is that caliber of cerebral arterioles are sensitive to several factors including the content of oxygen in the blood. Elevating the partial pressure of oxygen will lead to cerebral vasoconstriction that will counter the benefit that could be realized by increasing the oxygen supply. Carefully constructed clinical studies that are blinded and include sham control groups consistently showed no functional improvement associated with HBO2 treatment. Consequently, HBO2 treatment is not an accepted clinical treatment of stroke.

**Clinical studies of HBO2 treatment for stroke:** Two reports of clinical trials using repeated treatments of HBO2 to reduce the residual deficits of adults who survived strokes were published in 2013.[1, 15] The study [15] that incorporated adequate controls which satisfied National Institutes of Health (NIH) and Department of Veterans Affairs Office of Research Development (VAORD) criteria for well designed clinical trials reported that HBO2 treatment did not produce clinical improvement in the subjects. The other study [1] did not incorporate controls that would have been acceptable by either NIH or VAORD. There was no sham treatment control group. The control values were obtained by evaluating subjects during a period when they were receiving no treatments. That study reported some improvements in clinical outcomes that could have resulted from differences in subject expectations as to how they should perform on testing when they were or were not being actively treated. Another outcome that was reported was the functional images of the brains of subjects were different when they were receiving HBO2 compared to when they were not receiving HBO2. The changes in the functional imaging may represent alterations in blood flow patterns within the brains of subjects receiving HBO2. The imaging changes that were observed with HBO2 treatment did not continue when HBO2 treatment stopped. Consequently, when HBO2 was evaluated in a blinded and well controlled protocol it did not improve the clinical condition of subjects.

There were two reports of clinical studies using acute HBO2 intervention to reduce the cerebral injury resulting from stroke.[16, 17] These studies did not incorporate adequate controls. There were no sham-treatment control groups. The results of these studies were equivocal as to whether HBO2 improved the clinical outcome in subjects with acute strokes. One study analyzed the timing of the initiation of HBO2 after stroke onset and suggested that
Conclusions: HBO2 treatment for TBI and stroke. The 2010 report from PCS on HBO2 found that there was no evidence for clinical benefit from HBO2 for combat TBI. Additionally, the report suggested that VHA and DoD conduct an adequately controlled prospective study of HBO2 for combat TBI. VA and DoD collaborated on a carefully designed and robustly controlled and blinded study of HBO2 for combat-acquired TBI. The results of that collaborative research of VA and DoD was reported in 5 papers that were published between 2012 and 2014.[3-7] The findings of the VA/DoD studies of HBO2 for combat TBI clearly showed no benefit from using HBO2 to treat combat TBI. None of the well designed studies performed between 2010 and the present have shown any benefit from using HBO2 for treating TBI.[8, 9] The 2013 Israeli study did not have adequate controls.[2] A Cochrane review from 2012 reported that no well designed and executed study found any benefit from using HBO2 to treat TBI. Similarly for stroke, no well designed clinical study that incorporated adequate controls reported benefit from using HBO2 to treat stroke. The 2013 Israeli clinical study of HBO2 treatment for stroke did not have adequate controls. Therefore, HBO2 therapy remains a treatment that is not an accepted clinical treatment for either TBI of stroke.

References


2014 Follow-up to the 2010 Report on the use of Hyperbaric Oxygen Therapy for treating Veterans with Brain Injury

APPENDIX

Hyperbaric oxygen and adult TBI 1/2010 to 1/2014 (newest references first)

J Head Trauma Rehabil. 2014 Jan-Feb;29(1):11-20. Doi: 10.1097/HTR.0b013e3182a6aaf0.
The effect of hyperbaric oxygen on persistent postconcussion symptoms.
Cifu DX, Hart BB, West SL, Walker W, Carne W.
BACKGROUND: The high incidence of persistent postconcussion symptoms in service members with combat-related mild traumatic brain injury has prompted research in the use of hyperbaric oxygen (HBO2) for management.
OBJECTIVE: The effects of HBO2 on persistent postconcussion symptoms in 60 military service members with at least 1 combat-related mild traumatic brain injury were examined in a single-center, double-blind, randomized, sham-controlled, prospective trial at the Naval Medicine Operational Training Center at Naval Air Station Pensacola.
METHODS: Over a 10-week period, subjects received a series of 40, once-daily, hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA). During each session, subjects breathed 1 of 3 preassigned oxygen fractions (10.5%, 75%, or 100%) for 60 minutes, resulting in an oxygen exposure equivalent to breathing surface air, 100% oxygen at 1.5 ATA, or 100% oxygen at 2.0 ATA, respectively. Individual, subscale and total item responses on the Rivermead Postconcussion Symptom Questionnaire and individual and total Posttraumatic Disorder Checklist-Military Version were measured just prior to intervention and immediately postintervention.
RESULTS: Between-group testing of pre- and postintervention means revealed no significant differences on individual or total scores on the Posttraumatic Disorder Checklist-Military Version or Rivermead Postconcussion Symptom Questionnaire, demonstrating a successful randomization and no significant main effect for HBO2 at 1.5 or 2.0 ATA equivalent compared with the sham compression. Within-group testing of pre- and postintervention means revealed significant differences on several individual items for each group and difference in the Posttraumatic Disorder Checklist-Military Version total score for the 2.0 ATA HBO2 group.
DISCUSSION: The primary analyses of between group differences found no evidence of efficacy for HBO2. The scattered within group differences are threatened by Type 2 errors and could be explained by nonspecific effects.
CONCLUSION: This study demonstrated that HBO2 at either 1.5 or 2.0 ATA equivalent had no effect on postconcussion symptoms after mild traumatic brain injury when compared with sham compression.

Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial.
BACKGROUND:
Traumatic brain injury (TBI) is the leading cause of death and disability in the US. Approximately 70-90% of the TBI cases are classified as mild, and up to 25% of them
will not recover and suffer chronic neurocognitive impairments. The main pathology in these cases involves diffuse brain injuries, which are hard to detect by anatomical imaging yet noticeable in metabolic imaging. The current study tested the effectiveness of Hyperbaric Oxygen Therapy (HBOT) in improving brain function and quality of life in mTBI patients suffering chronic neurocognitive impairments.

METHODS AND FINDINGS:
The trial population included 56 mTBI patients 1-5 years after injury with prolonged post-concussion syndrome (PCS). The HBOT effect was evaluated by means of prospective, randomized, crossover controlled trial: the patients were randomly assigned to treated or crossover groups. Patients in the treated group were evaluated at baseline and following 40 HBOT sessions; patients in the crossover group were evaluated three times: at baseline, following a 2-month control period of no treatment, and following subsequent 2-months of 40 HBOT sessions. The HBOT protocol included 40 treatment sessions (5 days/week), 60 minutes each, with 100% oxygen at 1.5 ATA. "Mindstreams" was used for cognitive evaluations, quality of life (QOL) was evaluated by the EQ-5D, and changes in brain activity were assessed by SPECT imaging. Significant improvements were demonstrated in cognitive function and QOL in both groups following HBOT but no significant improvement was observed following the control period. SPECT imaging revealed elevated brain activity in good agreement with the cognitive improvements.

CONCLUSIONS:
HBOT can induce neuroplasticity leading to repair of chronically impaired brain functions and improved quality of life in mTBI patients with prolonged PCS at late chronic stage.

TRIAL REGISTRATION: ClinicalTrials.gov NCT00715052

Neurorehabil Neural Repair. 2013 Dec 26. [Epub ahead of print]
Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention.
Walker WC, Franke LM, Cifu DX, Hart BB.

BACKGROUND:
Mild traumatic brain injury (mTBI) and residual postconcussion syndrome (PCS) are common among combatants of the recent military conflicts in Iraq and Afghanistan. Hyperbaric oxygen (HBO2) is a proposed treatment but has not been rigorously studied for this condition.

OBJECTIVES:
In a secondary analysis, examine for possible effects on psychomotor (balance and fine motor) and cognitive performance 1 week after an HBO2 intervention in service members with PCS after mTBI.

METHODS:
A randomized, double-blind, sham control, feasibility trial comparing pretreatment and posttreatment was conducted in 60 male active-duty marines with combat-related mTBI and PCS persisting for 3 to 36 months. Participants were randomized to 1 of 3
preassigned oxygen fractions (10.5%, 75%, or 100%) at 2.0 atmospheres absolute (ATA), resulting in respective groups with an oxygen exposure equivalent to (1) breathing surface air (Sham Air), (2) 100% oxygen at 1.5 ATA (1.5 ATAO2), and (3) 100% oxygen at 2.0 ATA (2.0 ATAO2). Over a 10-week period, participants received 40 hyperbaric chamber sessions of 60 minutes each. Outcome measures, including computerized posturography (balance), grooved pegboard (fine motor speed/dexterity), and multiple neuropsychological tests of cognitive performance, were collected preintervention and 1-week postintervention.

RESULTS:
Despite the multiple sensitive cognitive and psychomotor measures analyzed at an unadjusted 5% significance level, this study demonstrated no immediate postintervention beneficial effect of exposure to either 1.5 ATAO2 or 2.0 ATAO2 compared with the Sham Air intervention.

CONCLUSIONS:
These results do not support the use of HBO2 to treat cognitive, balance, or fine motor deficits associated with mTBI and PCS.

KEYWORDS: cognition disorders, hyperbaric oxygenation, postconcussion syndrome, psychomotor performance, randomized controlled trial, traumatic brain injury


Hyperbaric oxygen for blast-related post-concussion syndrome: 3-month outcomes.
Importance: Mild traumatic brain injury (mTBI) and post-concussion syndrome (PCS) are common among military combatants. Hyperbaric oxygen (HBO2 ) is a proposed treatment for these conditions but it has not been rigorously studied. Objectives: Determine the effects by 3-months post-intervention of HBO2 at two commonly employed dosing levels to treat PCS. Also determine if specific subgroups may have benefited and if no overall effect is found if benefit is masked by other conditions.

Design: Randomized, double-blind, sham controlled study. Setting: Naval Air Station, Pensacola, Florida. Participants: 61 male Marines with history of mTBI and PCS.

Intervention: Forty, once daily, 60 minute, hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA) at one of three randomly pre-assigned oxygen fractions, resulting in respective blinded groups with an oxygen breathing exposure equivalent to 1) surface air (sham), 2) 100% oxygen at 1.5 ATA, or 3) 100% oxygen at 2.0 ATA. Main Outcome Measure: Rivermead Post-Concussion Questionnaire (RPQ-16) collected pre-compressions and at two later points. Results: Interaction of time by intervention group was not significant for improvement on the RPQ-16. Nor was there evidence of efficacy on the RPQ-16 for any subgroup. No significant time by intervention interaction was found for any functional, cognitive, or psychomotor secondary outcome measure at an unadjusted 0.05 significance level. Conclusions: Using a randomized control trial design and analysis including a sham, results show no evidence of efficacy by 3 months intervention to treat the symptom, cognitive, or behavioral sequelae of PCS after combat-related mTBI.
Reply: Department of Defense trials for hyperbaric oxygen and TBI: issues of study design and questionable conclusions.
Weaver LK, Cifu D, Hart B, Wolf G, Miller RS.

A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury.
Rockswold SB, Rockswold GL, Zaun DA, Liu J.

OBJECT:
Preclinical and clinical investigations indicate that the positive effect of hyperbaric oxygen (HBO2) for severe traumatic brain injury (TBI) occurs after rather than during treatment. The brain appears better able to use baseline O2 levels following HBO2 treatments. In this study, the authors evaluate the combination of HBO2 and normobaric hyperoxia (NBH) as a single treatment.

METHODS:
Forty-two patients who sustained severe TBI (mean Glasgow Coma Scale [GCS] score 5.7) were prospectively randomized within 24 hours of injury to either: 1) combined HBO2/NBH (60 minutes of HBO2 at 1.5 atmospheres absolute [ATA] followed by NBH, 3 hours of 100% fraction of inspired oxygen [FiO2] at 1.0 ATA) or 2) control, standard care. Treatments occurred once every 24 hours for 3 consecutive days. Intracranial pressure, surrogate markers for cerebral metabolism, and O2 toxicity were monitored. Clinical outcome was assessed at 6 months using the sliding dichotomized Glasgow Outcome Scale (GOS) score. Mixed-effects linear modeling was used to statistically test differences between the treatment and control groups. Functional outcome and mortality rates were compared using chi-square tests.

RESULTS:
There were no significant differences in demographic characteristics between the 2 groups. In comparison with values in the control group, brain tissue partial pressure of O2 (PO2) levels were significantly increased during and following combined HBO2/NBH treatments in both the noninjured and pericontusional brain (p < 0.0001). Microdialysate lactate/pyruvate ratios were significantly decreased in the noninjured brain in the combined HBO2/NBH group as compared with controls (p < 0.0078). The combined HBO2/NBH group's intracranial pressure values were significantly lower than those of the control group during treatment, and the improvement continued until the next treatment session (p < 0.0006). The combined HBO2/NBH group's levels of microdialysate glycerol were significantly lower than those of the control group in both noninjured and pericontusional brain (p < 0.001). The combined HBO2/NBH group's level of CSF F2-isoprostane was decreased at 6 hours after treatment as compared with that of controls, but the difference did not quite reach statistical significance (p = 0.0692). There was an absolute 26% reduction in mortality for the combined HBO2/NBH
group (p = 0.048) and an absolute 36% improvement in favorable outcome using the sliding dichotomized GOS (p = 0.024) as compared with the control group.

CONCLUSIONS:
In this Phase II clinical trial, in comparison with standard care (control treatment) combined HBO2/NBH treatments significantly improved markers of oxidative metabolism in relatively uninjured brain as well as pericontusional tissue, reduced intracranial hypertension, and demonstrated improvement in markers of cerebral toxicity. There was significant reduction in mortality and improved favorable outcome as measured by GOS. The combination of HBO2 and NBH therapy appears to have potential therapeutic efficacy as compared with the 2 treatments in isolation. CLINICAL TRIAL REGISTRATION NO.: NCT00170352 (ClinicalTrials.gov).

A prospective trial of hyperbaric oxygen for chronic sequelae after brain injury (HYBOBI).

OBJECTIVE:
Some practitioners advocate hyperbaric oxygen (HBO2) for sequelae following brain injury. This study assessed recruitment, tolerance and safety in preparation for a randomized clinical trial. Design: Prospective, open-label feasibility study.

SETTING:
Hyperbaric medicine department of a tertiary academic hospital. Participants: Participatory adult outpatients with problems from stroke (n=22), anoxia (13) or trauma (28) that occurred at least 12 months before enrollment, without contraindications to HBO2. Sixty-three participants enrolled in the study (21 females, 42 males). Age was 45 +/- 16 years (18-76) and time from injury was 6.9 +/- 7.1 years (1.0-29.3). Fifty-three completed the study intervention, and 55 completed the assessment battery.

METHODS:
Participants underwent 60 daily HBO2 sessions (1.5 atm abs, 100% oxygen, 60 minutes). Assessments were conducted at baseline, after the HBO2 course, and six months later. Main outcome measurements: The prime outcome was feasibility. To estimate the immediate and long-term effects of HBO2, we assessed neuropsychological measures, questionnaires, neurologic exam and physical functioning measures. Some participants also had pre- and post-HBO2 speech evaluation (n=27) and neuroimaging (n=17).

RESULTS:
The study met our a priori definition for feasibility for recruitment, but 44% required additional time to complete the 60 sessions (up to 105 days). HBO2-related adverse events were rare and not serious. Although many participants reported improvement in symptoms (51% memory, 51% attention/concentration, 48% balance/coordination, 45% endurance, 20% sleep) post-HBO2, and 93% reported that they would participate in the study again, no standardized testing showed clinically important improvement. In the small subset of those undergoing neuroimaging, apparent improvement was observed
in auditory functional MRI (8/13), MR spectroscopy (9/17) and brain perfusion by CT angiography (5/9).

CONCLUSIONS:
Conducting an HBO2 clinical trial in this population was feasible. Although many participants reported improvement, the lack of concurrent controls limits the strength of inferences from this trial, especially considering lack of change in standardized testing. The clinical relevance of neuroimaging changes is unknown. The findings of this study may indicate a need for caution when considering the broad application of HBO2 more than one year after brain injury due to stroke, severe TBI and anoxia, until there is more compelling evidence from carefully designed sham-controlled, blinded clinical trials.

Hyperbaric side effects in a traumatic brain injury randomized clinical trial.
Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O.

OBJECTIVE:
To catalog the side effects of 2.4 atmospheres absolute (atm abs) hyperbaric oxygen (HBO2) vs. sham on post-concussion symptoms in military service members with combat-related, mild traumatic brain injury (TBI).

METHODS:
Fifty subjects diagnosed with TBI were randomized to either a sham (1.3 atm abs breathing air) or treatment (2.4 atm abs breathing 100% oxygen) hyperbaric profile. Forty-eight subjects completed 30 exposures. Medical events during hyperbaric exposures were separately annotated by medical staff and chamber operators. After the blind was broken, events were segregated into the exposure groups.

RESULTS:
These side effects were observed as rate (sham/treatment): ear block (ear barotrauma) 5.51% (1.09%/5.91%), sinus squeeze 0.14% (0.0%/0.27%), and confinement anxiety 0.27% (0.27%/0.27%). Other conditions that occurred included: headache 0.61% (0.68%/0.54%); nausea 0.2% (0.14%/0.27%); numbness 0.07% (0%/0.13%); heartburn 0.07% (0.14%/0%); musculoskeletal chest pain 0.07% (0%/0.13%); latex allergy 0.07% (0.14%/0%); and hypertension 0.07% (0.14%/0%).

CONCLUSION:
This study demonstrated no major adverse events, such as pulmonary barotraumas, pulmonary edema or seizure. Given the infrequent, mild side effect profile, the authors feel the study demonstrated that hyperbaric oxygen therapy (HBO2T) was safe at a relatively high treatment pressure in TBI subjects, and these data can be used to evaluate the risk/benefit calculation when deciding to utilize HBO2T for treatment of various diseases in the TBI population.

Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury.
Bennett MH, Trytko B, Jonker B.

BACKGROUND:
Traumatic brain injury is a common health problem with significant effect on quality of life. Each year in the USA approximately 0.56% of the population suffer a head injury, with a case fatality rate of about 40% for severe injuries. These account for a high proportion of deaths in young adults. In the USA, 2% of the population live with long-term disabilities following head injuries. The major causes are motor vehicle crashes, falls, and violence (including attempted suicide). Hyperbaric oxygen therapy (HBOT) is the therapeutic administration of 100% oxygen at environmental pressures greater than 1 atmosphere absolute (ATA). This involves placing the patient in an airtight vessel, increasing the pressure within that vessel, and administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased partial pressure of oxygen to the tissues. HBOT can improve oxygen supply to the injured brain, reduce the swelling associated with low oxygen levels and reduce the volume of brain that will ultimately perish. It is, therefore, possible that adding HBOT to the standard intensive care regimen may reduce patient death and disability. However, a concern for patients and families is that using HBOT may result in preventing a patient from dying only to leave them in a vegetative state, entirely dependent on medical care. There are also some potential adverse effects of the therapy, including damage to the ears, sinuses and lungs from the effects of the pressure and oxygen poisoning, so the benefits and risks of the therapy need to be carefully evaluated.

OBJECTIVES:
To assess the effects of adjunctive HBOT for traumatic brain injury.

SEARCH METHODS:
We searched CENTRAL, MEDLINE, EMBASE, CINAHL and DORCTHIM electronic databases. We also searched the reference lists of eligible articles, handsearched relevant journals and contacted researchers. All searches were updated to March 2012.

SELECTION CRITERIA:
Randomised studies comparing the effect of therapeutic regimens which included HBOT with those that did not, for people with traumatic brain injury.

DATA COLLECTION AND ANALYSIS:
Three authors independently evaluated trial quality and extracted data.

MAIN RESULTS:
Seven studies are included in this review, involving 571 people (285 receiving HBOT and 286 in the control group). The results of two studies indicate use of HBOT results in a statistically significant decrease in the proportion of people with an unfavourable outcome one month after treatment using the Glasgow Outcome Scale (GOS) (relative risk (RR) for unfavourable outcome with HBOT 0.74, 95% CI 0.61 to 0.88, \( P = 0.001 \)). This five-point scale rates the outcome from one (dead) to five (good recovery); an 'unfavourable' outcome was considered as a score of one, two or three. Pooled data from final follow-up showed a significant reduction in the risk of dying when HBOT was used (RR 0.69, 95% CI 0.54 to 0.88, \( P = 0.003 \)) and suggests we would have to treat seven patients to avoid one extra death (number needed to treat (NNT) 7, 95% CI 4 to 22). Two trials suggested favourably lower intracranial pressure in people receiving HBOT and in whom myringotomies had been performed. The results from one study suggested a mean difference (MD) with myringotomy of -8.2 mmHg (95% CI -14.7 to -
1.7 mmHg, \( P = 0.01 \)). The Glasgow Coma Scale (GCS) has a total of 15 points, and two small trials reported a significant improvement in GCS for patients treated with HBOT (MD 2.68 points, 95%CI 1.84 to 3.52, \( P < 0.0001 \)), although these two trials showed considerable heterogeneity (I(2) = 83%). Two studies reported an incidence of 13% for significant pulmonary impairment in the HBOT group versus 0% in the non-HBOT group (\( P = 0.007 \)). In general, the studies were small and carried a significant risk of bias. None described adequate randomisation procedures or allocation concealment, and none of the patients or treating staff were blinded to treatment.

AUTHORS’ CONCLUSIONS:

In people with traumatic brain injury, while the addition of HBOT may reduce the risk of death and improve the final GCS, there is little evidence that the survivors have a good outcome. The improvement of 2.68 points in GCS is difficult to interpret. This scale runs from three (deeply comatose and unresponsive) to 15 (fully conscious), and the clinical importance of an improvement of approximately three points will vary dramatically with the starting value (for example an improvement from 12 to 15 would represent an important clinical benefit, but an improvement from three to six would leave the patient with severe and highly dependent impairment). The routine application of HBOT to these patients cannot be justifiable from this review. Given the modest number of patients, methodological shortcomings of included trials and poor reporting, the results should be interpreted cautiously. An appropriately powered trial of high methodological rigour is required to define which patients, if any, can be expected to benefit most from HBOT.

The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury.

Wolf G, Cifu D, Baugh L, Carne W, Profenna L.

In this single-center, double-blind, randomized, sham-controlled, prospective trial at the U.S. Air Force School of Aerospace Medicine, the effects of 2.4 atmospheres absolute (ATA) hyperbaric oxygen (\( \text{HBO}_2 \)) on post-concussion symptoms in 50 military service members with at least one combat-related, mild traumatic brain injury were examined. Each subject received 30 sessions of either a sham compression (room air at 1.3 ATA) or \( \text{HBO}_2 \) treatments at 2.4 ATA over an 8-week period. Individual and total symptoms scores on Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT®) and composite scores on Post-traumatic Disorder Check List-Military Version (PCL-M) were measured just prior to intervention and 6 weeks after completion of intervention. Difference testing of post-intervention means between the sham-control and \( \text{HBO}_2 \) group revealed no significant differences on the PCL-M composite score (\( t=0.205, p=0.84 \)) or on the ImPACT total score (\( t=0.943, p=0.35 \)), demonstrating no significant effect for \( \text{HBO}_2 \) at 2.4 ATA. PCL-M composite scores and ImPACT total scores for sham-control and \( \text{HBO}(2) \) groups revealed significant improvement over the course of the study for both the sham-control group (\( t=3.76, p=0.001 \)) and the \( \text{HBO}_2 \) group (\( t=3.90, p=0.001 \)), demonstrating no significant \( \text{HBO}_2 \) effect. Paired t-test results revealed 10 ImPACT scale scores in the sham-control group improved from pre- to
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post-testing, whereas two scale scores significantly improved in the HBO₂ group. One PCL-M measure improved from pre- to post-testing in both groups. This study showed that HBO₂ at 2.4 ATA pressure had no effect on post-concussive symptoms after mild TBI.

Comment in
Hyperbaric oxygen, mild traumatic brain injury, and study design: an elusive target. [J Neurotrauma. 2013]
Hyperbaric oxygen therapy no better than sham in improving post-concussion symptoms following mild traumatic brain injury. [Diving Hyperb Med. 2013]
Hyperbaric oxygen therapy for post-concussion syndrome: contradictory conclusions from a study mischaracterized as sham-controlled. [J Neurotrauma. 2013]

Hyperbaric oxygen for post-concussion syndrome: design of Department of Defense clinical trials.
Weaver LK, Cifu D, Hart B, Wolf G, Miller S.
The current wars in the Middle East have resulted in between 10-20% of U.S. service members with mild traumatic brain injury (mTBI). While anecdotal reports have associated hyperbaric oxygen (HBO₂) with improved outcomes after mTBI, controlled research is lacking. The Department of Defense (DoD), in collaboration with the Department of Veterans Affairs (DVA), has a comprehensive program examining this issue. The DoD’s four randomized controlled trials will enroll a total of 242 service members with post-concussion syndrome and expose them to a range of control, sham and HBO2 conditions for 40 sessions over a period of eight to 11 weeks. Compression pressures will range from 1.2 atm abs (sham) to 2.4 atm abs, and oxygen concentration will range from room air (sham and control) to 100%. Outcomes measures include both subjective and objective measures performed at baseline, at exposure completion, and at three to 12 months’ follow-up. This integrated program of clinical trials investigating the efficacy of HBO₂ in service members with persistent symptoms following mTBI exposure will be important to define practice guidelines and, if needed, for the development of definitive clinical trials in this population.

Comment in
Department of Defense trials for hyperbaric oxygen and TBI: issues of study design and questionable conclusions. [Undersea Hyperb Med. 2013]
Reply: Department of Defense trials for hyperbaric oxygen and TBI: issues of study design and questionable conclusions. [Undersea Hyperb Med. 2013]
Hyperbaric oxygen therapy no better than sham in improving post-concussion symptoms following mild traumatic brain injury. [Diving Hyperb Med. 2013]

Tension pneumocephalus as a complication of hyperbaric oxygen therapy in a patient with chronic traumatic brain injury.
Lee LC, Lieu FK, Chen YH, Hung TH, Chen SF.
Although hyperbaric oxygen therapy has not been accepted as a standard therapy for traumatic brain injuries, it has been used, along with rehabilitative exercises, for traumatic brain injuries, and the standard protocol has a low risk of complications. We report a case of chronic traumatic brain injury that progressed to tension pneumocephalus after hyperbaric oxygen therapy. The patient was a 25-yr-old man who presented with left occipital bone fracture and subarachnoid and subdural hemorrhage after being hit by a car. He underwent craniectomy to remove the hematoma and cerebrospinal fluid diversion with a ventriculoperitoneal shunt for the treatment of hydrocephalus. Fifteen months after the trauma, the patient received hyperbaric oxygen therapy to promote functional recovery. Tension pneumocephalus developed after the first session of hyperbaric oxygen therapy, and immediate burr hole drainage followed by ligation of the ventriculoperitoneal shunt was performed. The patient's consciousness recovered gradually, and he was discharged home. We suggest that patients with unrepaired skull base fracture and cerebrospinal fluid diversion should be carefully evaluated before receiving hyperbaric oxygen therapy.

Use of hyperbaric oxygen in traumatic brain injury: retrospective analysis of data of 20 patients treated at a tertiary care centre.
Sahni T, Jain M, Prasad R, Sogani SK, Singh VP.
Traumatic brain injury (TBI) related impact results in a permanent need for help in performing daily activities. Standard treatment consists of removing the cause, restore perfusion, support metabolic requirement and limit inflammatory and oxidative damage. Hyperbaric oxygen therapy (HBOT) is one such newer promising treatment that enhances neurological recovery to some extent. HBOT is intermittent inhalation of 100% oxygen at greater than normal atmospheric pressure and is internationally accepted for its role in well-defined indications. It is hypothesised that HBO has a role in reviving 'idling neurons', also called the ischemic penumbra defined as area of reduced cerebral blood flow, abolished synaptic activity but preserved structural integrity. We carried out a retrospective analysis of medical records of 20 patients of TBI who had been treated with HBOT in addition to standard management. These were placed in Group A (test group) and received at least 30 sessions of HBO along with standard treatment. The patients were assessed along the Disability Rating Scale (DRS), Glasgow coma scale (GCS) and Rancho Los Amigos Scale (RLAS). Another 20 patients of TBI, matched in age and severity of brain injury, who received standard treatment but not HBOT, were selected as the control group (Group B). Assessment on the DRS showed maximum improvement in patients with scores of 22-24 (vegetative state). The percentage of patients in the test group fell from 45% to 5% whereas only 20% patients in Group B had similar progress. After the treatment, a significantly higher proportion of HBOT treated subjects showed a good response in cognitive functions, as
measured by RLA. In group A, 90% patients had a score of ≤ 3 and in Group B 95% had a similar score, which improved to ≥ 3 in 60% patients versus 30% patients respectively. In both groups maximum patients are in 1-6 months post-injury category and within the groups this category showed the greatest recovery, with a greater improvement in the test group as compared to control group.

A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury.
OBJECT:
Oxygen delivered in supraphysiological amounts is currently under investigation as a therapy for severe traumatic brain injury (TBI). Hyperoxia can be delivered to the brain under normobaric as well as hyperbaric conditions. In this study the authors directly compare hyperbaric oxygen (HBO2) and normobaric hyperoxia (NBH) treatment effects.
METHODS:
Sixty-nine patients who had sustained severe TBIs (mean Glasgow Coma Scale Score 5.8) were prospectively randomized to 1 of 3 groups within 24 hours of injury: 1) HBO2, 60 minutes of HBO(2) at 1.5 ATA; 2) NBH, 3 hours of 100% fraction of inspired oxygen at 1 ATA; and 3) control, standard care. Treatments occurred once every 24 hours for 3 consecutive days. Brain tissue PO(2), microdialysis, and intracranial pressure were continuously monitored. Cerebral blood flow (CBF), arteriovenous differences in oxygen, cerebral metabolic rate of oxygen (CMRO2), CSF lactate and F2-isoprostane concentrations, and bronchial alveolar lavage (BAL) fluid interleukin (IL)-8 and IL-6 assays were obtained pretreatment and 1 and 6 hours posttreatment. Mixed-effects linear modeling was used to statistically test differences among the treatment arms as well as changes from pretreatment to posttreatment.
RESULTS:
In comparison with values in the control group, the brain tissue PO2 levels were significantly increased during treatment in both the HBO2 (mean +/- SEM, 223 +/- 29 mm Hg) and NBH (86 +/- 12 mm Hg) groups (p < 0.0001) and following HBO2 until the next treatment session (p = 0.003). Hyperbaric O2 significantly increased CBF and CMRO2 for 6 hours (p < or = 0.01). Cerebrospinal fluid lactate concentrations decreased posttreatment in both the HBO2 and NBH groups (p < 0.05). The dialysate lactate levels in patients who had received HBO2 decreased for 5 hours posttreatment (p = 0.017). Microdialysis lactate/pyruvate (L/P) ratios were significantly decreased posttreatment in both HBO2 and NBH groups (p < 0.05). Cerebral blood flow, CMRO2, microdialysate lactate, and the L/P ratio had significantly greater improvement when a brain tissue PO2 > or = 200 mm Hg was achieved during treatment (p < 0.01). Intracranial pressure was significantly lower after HBO2 until the next treatment session (p < 0.001) in comparison with levels in the control group. The treatment effect persisted over all 3 days. No increase was seen in the CSF F2-isoprostane levels, microdialysate
glycerol, and BAL inflammatory markers, which were used to monitor potential O2 toxicity.

CONCLUSIONS:
Hyperbaric O2 has a more robust posttreatment effect than NBH on oxidative cerebral metabolism related to its ability to produce a brain tissue PO2 \( \geq 200 \) mm Hg. However, it appears that O2 treatment for severe TBI is not an all or nothing phenomenon but represents a graduated effect. No signs of pulmonary or cerebral O2 toxicity were present.

**Clinical studies of HBOT and stroke**
A prospective trial of hyperbaric oxygen for chronic sequelae after brain injury (HYBOBI).

OBJECTIVE:
Some practitioners advocate hyperbaric oxygen (HBO2) for sequelae following brain injury. This study assessed recruitment, tolerance and safety in preparation for a randomized clinical trial. Design: Prospective, open-label feasibility study.

SETTING:
Hyperbaric medicine department of a tertiary academic hospital. Participants: Participatory adult outpatients with problems from stroke (n=22), anoxia (13) or trauma (28) that occurred at least 12 months before enrollment, without contraindications to HBO2. Sixty-three participants enrolled in the study (21 females,42 males). Age was 45 +/- 16 years (18-76) and time from injury was 6.9 +/- 7.1 years (1.0-29.3). Fifty-three completed the study intervention, and 55 completed the assessment battery.

METHODS:
Participants underwent 60 daily HBO2 sessions (1.5 atm abs, 100% oxygen, 60 minutes). Assessments were conducted at baseline, after the HBO2 course, and six months later. Main outcome measurements: The prime outcome was feasibility. To estimate the immediate and long-term effects of HBO2, we assessed neuropsychological measures, questionnaires, neurologic exam and physical functioning measures. Some participants also had pre- and post-HBO2 speech evaluation (n=27) and neuroimaging (n=17).

RESULTS:
The study met our a priori definition for feasibility for recruitment, but 44% required additional time to complete the 60 sessions (up to 105 days). HBO2-related adverse events were rare and not serious. Although many participants reported improvement in symptoms (51% memory, 51% attention/concentration, 48% balance/coordination, 45% endurance, 20% sleep) post-HBO2, and 93% reported that they would participate in the study again, no standardized testing showed clinically important improvement. In the small subset of those undergoing neuroimaging, apparent improvement was observed in auditory functional MRI (8/13), MR spectroscopy (9/17) and brain perfusion by CT angiography (5/9).
CONCLUSIONS:
Conducting an HBO2 clinical trial in this population was feasible. Although many participants reported improvement, the lack of concurrent controls limits the strength of inferences from this trial, especially considering lack of change in standardized testing. The clinical relevance of neuroimaging changes is unknown. The findings of this study may indicate a need for caution when considering the broad application of HBO2 more than one year after brain injury due to stroke, severe TBI and anoxia, until there is more compelling evidence from carefully designed sham-controlled, blinded clinical trials


BACKGROUND:
Recovery after stroke correlates with non-active (stunned) brain regions, which may persist for years. The current study aimed to evaluate whether increasing the level of dissolved oxygen by Hyperbaric Oxygen Therapy (HBOT) could activate neuroplasticity in patients with chronic neurologic deficiencies due to stroke.

METHODS AND FINDINGS:
A prospective, randomized, controlled trial including 74 patients (15 were excluded). All participants suffered a stroke 6-36 months prior to inclusion and had at least one motor dysfunction. After inclusion, patients were randomly assigned to "treated" or "cross" groups. Brain activity was assessed by SPECT imaging; neurologic functions were evaluated by NIHSS, ADL, and life quality. Patients in the treated group were evaluated twice: at baseline and after 40 HBOT sessions. Patients in the cross group were evaluated three times: at baseline, after a 2-month control period of no treatment, and after subsequent 2-months of 40 HBOT sessions. HBOT protocol: Two months of 40 sessions (5 days/week), 90 minutes each, 100% oxygen at 2 ATA. We found that the neurological functions and life quality of all patients in both groups were significantly improved following the HBOT sessions while no improvement was found during the control period of the patients in the cross group. Results of SPECT imaging were well correlated with clinical improvement. Elevated brain activity was detected mostly in regions of live cells (as confirmed by CT) with low activity (based on SPECT) - regions of noticeable discrepancy between anatomy and physiology.

CONCLUSIONS:
The results indicate that HBOT can lead to significant neurological improvements in post stroke patients even at chronic late stages. The observed clinical improvements imply that neuroplasticity can still be activated long after damage onset in regions where there is a brain SPECT/CT (anatomy/physiology) mismatch

The role of hyperbaric oxygen therapy (HBOT) in the treatment of acute ischemic stroke is controversial. This prospective study assessed the efficacy and safety of HBOT as adjuvant treatment on 46 acute ischemic stroke in patients who did not receive thrombolytic therapy. The HBOT group (n = 16) received conventional medical treatment with 10 sessions of adjunctive HBOT within 3-5 days after stroke onset, while the control group (n = 30) received the same treatment but without HBOT. Early (around two weeks after onset) and late (one month after onset) outcomes (National Institutes of Health Stroke Scale, NIHSS scores) and efficacy (changes of NIHSS scores) of HBOT were evaluated. The baseline clinical characteristics were similar in both groups. Both early and late outcomes of the HBOT group showed significant difference (P ≤ 0.001). In the control group, there was only significant difference in early outcome (P = 0.004). For early efficacy, there was no difference when comparing changes of NIHSS scores between the two groups (P = 0.140) but there was statistically significant difference when comparing changes of NIHSS scores at one month (P ≤ 0.001). The HBOT used in this study may be effective for patients with acute ischemic stroke and is a safe and harmless adjunctive treatment.

Treatment of acute stroke with hyperbaric oxygen: time window for efficacy.
McCormick JG, Houle TT, Saltzman HA, Whaley RC, Roy RC.
We conducted a retrospective statistical analysis of the Heyman, Saltzman, Whalen 1966 study of 22 stroke patients treated with hyperbaric oxygen (HBO2) -- 13 of them one to five hours post-stroke. We examined patients who received HBO2 treatment within seven hours post-stroke. An exploratory logistic regression analysis examining the influence of time post-stroke, time in chamber and dose of HBO2, range 2.02 atmospheres absolute (ATA) to 3.04 ATA, was conducted. Only time post-stroke was a significant influence for recovery, with each passing hour decreasing the chance of at least partial transient recovery by 62% - odds ratio: 0.38 (95% CI: 0.15 -0.95). p = 0.039. In the one- to five-hour group of 13 patients, nine (41% of 22) had recovery or recovery with relapse. This represented 69% (+/- 25% SE) of this time frame. Only two of the nine had permanent recovery. Past six hours poststroke, only one patient (11% +/- 21% SE) had partial recovery with relapse. The other eight past six hours had no recovery at all. The first three hours post-stroke HBO2 administration has the most promise for efficacy and improvement of rtPA therapy. HBO2 may also prove to be a useful challenge pre-rtPA administration to assess the risk-benefit ratio for giving rtPA.

Hyperbaric oxygen and stroke – experimental studies
Preconditioning provides neuroprotection in models of CNS disease: Paradigms and clinical significance.
Stetler RA1, Leak RK2, Gan Y3, Li P3, Hu X4, Jing Z4, Chen J1, Zigmond MJ3, Gao Y5.
Preconditioning is a phenomenon in which brief episodes of a sublethal insult induce robust protection against subsequent lethal injuries. Preconditioning has been observed in multiple organisms and can occur in the brain as well as other tissues. Extensive animal studies suggest that the brain can be preconditioned to resist acute injuries, such as ischemic stroke, neonatal hypoxia/ischemia, trauma, and agents that are used in models of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Effective preconditioning stimuli are numerous and diverse, ranging from transient ischemia, hypoxia, hyperbaric oxygen, hypothermia and hyperthermia, to exposure to neurotoxins and pharmacological agents. The phenomenon of "cross-tolerance," in which a sublethal stress protects against a different type of injury, suggests that different preconditioning stimuli may confer protection against a wide range of injuries. Research conducted over the past few decades indicates that brain preconditioning is complex, involving multiple effectors such as metabolic inhibition, activation of extra- and intracellular defense mechanisms, a shift in the neuronal excitatory/inhibitory balance, and reduction in inflammatory sequelae. An improved understanding of brain preconditioning should help us identify innovative therapeutic strategies that prevent or at least reduce neuronal damage in susceptible patients. In this review, we focus on the experimental evidence of preconditioning in the brain and systematically survey the models used to develop paradigms for neuroprotection, and then discuss the clinical potential of brain preconditioning.

Attenuating brain inflammation, ischemia, and oxidative damage by hyperbaric oxygen in diabetic rats after heat stroke.
Lee KL, Niu KC, Lin MT, Niu CS.
BACKGROUND/PURPOSE:
Alternating hypothalamic-pituitary-adrenal axis mechanisms would lead to multiple organs dysfunction or failure. Herein, we attempt to assess whether hypothalamic inflammation and ischemic and oxidative damage that occurred during heatstroke (HS) can be affected by hyperbaric oxygen (HBO₂) therapy in streptozotocin-induced diabetic rats.
METHODS:
In this study, anesthetized diabetic rats, immediately after the onset of HS, were divided into two major groups and given the normobaric air (21% O₂ at 1.0 atmospheres absolute) or HBO₂ (100% O₂ at 2.0 atmospheres absolute). HS was induced by exposing the animals to heat stress (43°C). Another group of anesthetized diabetic rats was kept at normothermic state and used as controls.
RESULTS:
The survival time values for the HBO2-treated HS-diabetic rats increased from the control values of 78-82 minutes to new values of 184-208 minutes. HBO2 therapy caused a reduction of HS-induced cellular ischemia (e.g., increased cellular levels of glutamate and lactate/pyruvate ratio), hypoxia (e.g., decreased cellular levels of PO2), inflammation (e.g., increased cellular levels of interleukin-1β, tumor necrosis factor-alpha, interleukin-6, and myeloperoxidase), and oxidative damage (e.g., increased values of nitric oxide, 2,3-dihydroxybenzoic acid, glycerol, and neuronal damage score) in the hypothalamus of the diabetic rats.

CONCLUSION:
Our results suggest that, in diabetic animals, HBO2 therapy may improve outcomes of HS in part by reducing heat-induced activated inflammation and ischemic and oxidative damage in the hypothalamus and other brain regions.

Hyperglycemia dramatically aggravates brain infarct and hemorrhagic transformation (HT) after ischemic stroke. Oxidative stress and matrix metalloproteinases (MMPs) play an important role in the pathophysiology of HT. Hyperbaric oxygen preconditioning (HBO-PC) has been proved to decrease oxidative stress and has been demonstrated to be neuroprotective in experimental stroke models. The present study determined whether HBO-PC would ameliorate HT by a pre-ischemic increase of reactive oxygen species (ROS) generation, and a suppression of MMP-2 and MMP-9 in hyperglycemic middle cerebral artery occlusion (MCAO) rats. Rats were pretreated with HBO (100% O2, 2.5 atmosphere absolutes) 1 h daily for 5 days before MCAO. Acute hyperglycemia was induced by an injection of 50% dextrose. Neurological deficits, infarction volume and hemorrhagic volume were assessed 24 h and 7 days after ischemia. ROS scavenger N-acetyl cysteine (NAC), hypoxia-inducible factor-1α (HIF-1α), inhibitor 2-methoxyestradiol (2ME2) and activator cobalt chloride (CoCl2), and MMP inhibitor SB3CT were administrated for mechanism study. The activity of MMP-2 and MMP-9, and the expression HIF-1α were measured. HBO-PC improved neurological deficits, and reduced hemorrhagic volume; the expression of HIF-1α was significantly decreased, and the activity of MMP-2 and MMP-9 was reduced by HBO-PC compared with vehicle group. Our results suggested that HBO-PC attenuated HT via decreasing HIF-1α and its downstream MMP-2 and MMP-9 in hyperglycemic MCAO rats.

Long course hyperbaric oxygen stimulates neurogenesis and attenuates inflammation after ischemic stroke.
Lee YS, Chio CC, Chang CP, Wang LC, Chiang PM, Niu KC, Tsai KJ.
Several studies have provided evidence with regard to the neuroprotection benefits of hyperbaric oxygen (HBO) therapy in cases of stroke, and HBO also promotes bone
marrow stem cells (BMSCs) proliferation and mobilization. This study investigates the influence of HBO therapy on the migration of BMSCs, neurogenesis, gliosis, and inflammation after stroke. Rats that sustained transient middle cerebral artery occlusion (MCAO) were treated with HBO three weeks or two days. The results were examined using a behavior test (modified neurological severity score, mNSS) and immunostaining to evaluate the effects of HBO therapy on migration of BMSCs, neurogenesis, and gliosis, and expression of neurotrophic factors was also evaluated. There was a lower mNSS score in the three-week HBO group when compared with the two-day HBO group. Mobilization of BMSCs to an ischemic area was more improved in long course HBO treatments, suggesting the duration of therapy is crucial for promoting the homing of BMSCs to ischemic brain by HBO therapies. HBO also can stimulate expression of trophic factors and improve neurogenesis and gliosis. These effects may help in neuronal repair after ischemic stroke, and increasing the course of HBO therapy might enhance therapeutic effects on ischemic stroke.


Serum leptin levels decrease after permanent MCAo in the rat and remain unaffected by delayed hyperbaric oxygen therapy.

Mu J, Ostrowski RP, Krafft PR, Tang J, Zhang JH.

Hyperbaric oxygen therapy (HBOT), referring to the medical use of oxygen at a level higher than atmospheric pressure, exerts neuroprotective effects after ischemic stroke via various mechanisms. It has been demonstrated that HBOT modulates the synthesis and degradation of hormones. Leptin, an adipose derived hormone, has been found to confer neuroprotection following experimental stroke. However, it is not known whether HBOT alters leptin concentrations after permanent middle cerebral artery occlusion (pMCAo) in the rat. In this present study, we aimed to investigate the effect of HBOT on the serum concentration of leptin in rats subjected to pMCAo. HBOT was initiated 48 hrs after experimental pMCAo, at 2.5 atmospheres absolutes with 100% oxygen, 1 hr a day for 10 consecutive days. Body weight, neurobehavioral deficits and infarct size were evaluated. Blood was collected on day 1 and day 16 following HBOT. Serum leptin concentrations were measured with ELISA. Delayed HBOT reduced infarct size and improved neurobehavioral scores. Decreased serum levels of leptin were found in treated and untreated pMCAo animals, compared to the sham group on day 1 (P > 0.05) and day 16 (P < 0.05). However, no statistical significance was found between HBOT and the air group. We concluded that the neuroprotective effects of delayed HBOT in pMCAo rats were unlikely to be exerted through changes in the serum concentration of leptin.


Delayed hyperbaric oxygen therapy induces cell proliferation through stabilization of cAMP responsive element binding protein in the rat model of MCAo-induced ischemic brain injury.

Mu J, Ostrowski RP, Soejima Y, Rolland WB, Krafft PR, Tang J, Zhang JH.
Treatments that could extend the therapeutic window of opportunity for stroke patients are urgently needed. Early administration of hyperbaric oxygen therapy (HBOT) has been proven neuroprotective in the middle cerebral artery occlusion (MCAo) in rodents. Our aim was to determine: 1) whether delayed HBOT after permanent MCAo (pMCAo) can still convey neuroprotection and restorative cell proliferation, and 2) whether these beneficial effects rely on HBO-induced activation of protein phosphatase-1γ (PP1-γ) leading to a decreased phosphorylation and ubiquitination of CREB and hence its stabilization. The experiments were performed in one hundred thirty-two male Sprague-Dawley rats with the body weight ranging from 240 to 270 g. Permanent MCAo was induced with the intraluminal filament occluding the right middle cerebral artery (MCA). In the first experiment, HBOT (2.5 ATA, 1h daily for 10 days) was started 48 h after pMCAo. Neurobehavioral deficits and infarct size as well as cyclic AMP response element-binding protein (CREB) expression and BrdU-DAB staining in the hippocampus and the peri-infarct region were evaluated on day 14 and day 28 post-MCAo. In the second experiment, HBOT (2.5 ATA, 1h) was started 3h after pMCAo. The effects of CREB siRNA or PP1-γ siRNA on HBO-induced infarct size alterations and target protein expression were studied. HBOT started with 48 h delay reduced infarct size, ameliorated neurobehavioral deficits and increased protein expression of CREB, resulting in increased cell proliferations in the hippocampus and peri-infarct region, on day 14 and day 28 post-MCAo. In the acute experiment pMCAo resulted in cerebral infarction and functional deterioration and reduced brain expression of PP1-γ, which led to increased phosphorylation and ubiquitination of CREB 24h after MCAo. However HBOT administered 3h after ischemia reversed these molecular events and resulted in CREB stabilization, infarct size reduction and neurobehavioral improvement. Gene silencing with CREB siRNA or PP1-γ siRNA reduced acute beneficial effects of HBO. In conclusion, delayed daily HBOT presented as potent neuroprotectant in pMCAo rats, increased CREB expression and signaling activity, and bolstered regenerative type cell proliferation in the injured brain. As shown in the acute experiment these effects of HBO were likely to be mediated by reducing ubiquitin-dependent CREB degradation owing to HBO-induced activation of PP1γ.
investigated. Rats underwent middle cerebral artery occlusion and were assigned to control, tPA or tPA+HBO. Twenty-four hours, 7, 14 and 28 days were determined as observation time points. The accumulation of macrophage-like cells was semiquantitatively assessed by CD68 staining in the ischaemic area and ischaemic border zone, and linked to the clinical course. CD11b, ionized calcium binding adaptor molecule 1 (Iba), glial fibrillary acidic protein (GFAP) and Neuronal Nuclei (NeuN) were applied to reveal delayed glial and neuronal alterations. In all groups, the accumulation of macrophage-like cells increased distinctly from 24 hours to 7 days post ischaemia. tPA+HBO tended to decrease macrophage-like cell accumulation at day 14 and 28. Overall, a trend towards an association of increased accumulation and pronounced reduction of the neurological deficit was found. Concerning delayed inflammatory reactions, an activation of microglia and astrocytes with co-occurring neuronal loss was observed on day 28. Thereby, astrogliosis was found circularly in contrast to microglial activation directly in the ischaemic area. This study supports previous data on long-lasting inflammatory processes following experimental stroke, and additionally provides region-specific details on glial reactions. The tendency towards a decreasing macrophage-like cell accumulation after tPA+HBO needs to be discussed critically since neuroprotective properties were recently ascribed to long-term inflammatory processes.

Hyperbaric oxygen preconditioning attenuates hyperglycemia enhanced hemorrhagic transformation after transient MCAO in rats.
Soejima Y, Ostrowski RP, Manaenko A, Fujii M, Tang J, Zhang JH.
BACKGROUND:
Hemorrhagic transformation (HT) can be a devastating complication of ischemic stroke. Hyperbaric oxygen preconditioning (HBO-PC) has been shown to improve blood-brain barrier (BBB) permeability in stroke models. The purpose of this study is to examine whether HBO-PC attenuates HT after focal cerebral ischemia, and to investigate whether the mechanism of HBO-PC against HT includes up-regulation of antioxidants in hyperglycemic rats.
METHODS:
Male Sprague-Dawley rats (280-320 g) were divided into the following groups: sham, middle cerebral artery occlusion (MCAO) for 2 h, and MCAO treated with HBO-PC. HBO-PC was conducted giving 100% oxygen at 2.5 atm absolute (ATA), for 1 h at every 24 h interval for 5 days. At 24 h after the last session of HBO-PC, rats received an injection of 50% glucose (6 ml/kg intraperitoneally) and were subjected to MCAO 15 min later. At 24 h after MCAO, neurological behavior tests, infarct volume, blood-brain barrier permeability, and hemoglobin content were measured to evaluate the effect of HBO-PC. Western blot analysis of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) was evaluated at multiple time-points before and after MCAO.
RESULTS:
HBO-PC improved neurological behavior test, and reduced infarction volume. HT and Evans blue extravasation in the ipsilateral hemisphere at 24 h after MCAO. Western blot
analysis failed to demonstrate up-regulation of Nrf2 in HBO-PC group before and after MCAO. Paradoxically, HBO-PC decreased HO-1 expression at 24 h after MCAO, as compared with htMCAO group.

CONCLUSIONS:
HBO-PC improved neurological deficits, infarction volume, BBB disruption, and HT after focal cerebral ischemia. However, its mechanism against focal cerebral ischemia and HT may not include activation of Nrf2 and subsequent HO-1 expression.

Long-lasting neuronal loss following experimental focal cerebral ischemia is not affected by combined administration of tissue plasminogen activator and hyperbaric oxygen. Hobohm C, Laignel F, Kacza J, Küppers-Tiedt L, Heindl M, Schneider D, Grosche J, Härtig W, Michalski D.

Acute focal cerebral ischemia and consecutive energy failure are accompanied by neuronal death in regions with impaired cerebral blood flow. Several translational attempts of potential neuroprotective agents have failed, hence extended perspectives are required regarding the regional differences of neuronal impairment and glial involvement by using clinically relevant stroke models. This study aimed on neuronal loss following experimental focal cerebral ischemia, considering tissue plasminogen activator (tPA) as established treatment in stroke and hyperbaric oxygenation (HBO) as potential neuroprotective co-treatment. Wistar rats were subjected to embolic middle cerebral artery occlusion and underwent either treatment with tPA only, combined tPA+HBO, or no treatment. Neuronal impairment was assessed by Neuronal Nuclei (NeuN) staining in 4 ischemia-related areas and at 4 different time points after stroke induction (24hours, 7, 14 and 28 days). Additionally, spatial relationships between neuronal loss and gliosis were revealed by triple fluorescence staining of neurons, astrocytes and microglia, comparing the ipsi- and contra-lesional hemisphere. Analyzing the ischemic injury in general, a shell-like distribution of neuronal damage was observed, starting in the ischemic core and diminishing over the general ischemic area to the ischemic border zone and the primary non-affected area. This pattern remained detectable up to 4weeks after ischemia induction. Surprisingly, tPA and tPA+HBO did not markedly affect the post-ischemic course of neuronal impairment. Further studies are needed to investigate the effects of treatment with tPA or potential neuroprotective agents on neuronal integrity, with emphasis on the separation of intact neurons from those undergoing apoptosis or necrosis

Oxygen therapy improves energy metabolism in focal cerebral ischemia. Sun L, Strelow H, Mies G, Veltkamp R.
Oxygen therapy (OT) with hyperbaric oxygen (HBO) or normobaric hyperoxia (NBO) improves the oxygenation of penumbral tissue in experimental ischemic stroke. However, whether this results in the improvement of energy metabolism is unclear. We
investigated the effect of both OTs on tissue acidosis and on ATP production. Beginning 25 min after filament middle cerebral artery occlusion (MCAO), mice breathed either air, 100% O$_2$ (NBO), or 100% O$_2$ at 3 ata (HBO) for 60 min. Regional tissue pH was measured using the umbelliferone fluorescence. Regional ATP concentration was depicted by substrate-specific bioluminescence. Severity of ischemia did not differ among groups in laser-Doppler flowmetry. Both NBO (70.1±14.0 mm$^3$) and, more effectively, HBO (57.2±11.9 mm$^3$) significantly reduced volume of tissue acidosis compared to air (89.4±4.0 mm$^3$), p<0.05). Topographically, acidosis was less pronounced in the medial striatum and in the cortical ischemic border areas. This resulted in significantly smaller volumes of ATP depletion (77.8±7.7 mm$^3$ in air, 61.4±15.2 mm$^3$ in NBO and 51.2±14.4 mm$^3$ in HBO; p<0.05). In conclusion, OT significantly improves energy metabolism in the border zones of focal cerebral ischemia which are the areas protected by OT in this model.


Combined systemic thrombolysis with alteplase and early hyperbaric oxygen therapy in experimental embolic stroke in rats: relationship to functional outcome and reduction of structural damage.


INTRODUCTION:
The only causal therapy in ischemic stroke is thrombolysis with recombinant tissue plasminogen activator (rtPA), but it is feasible only for few patients, and new therapies are needed. This study investigates the effects of systemic thrombolysis with rtPA combined with hyperbaric oxygen therapy (HBOT) in embolic stroke in rats.

METHODS:
In 22 male Wistar rats, an embolic ischemic stroke was induced. The animals were randomized to one of four groups: control, thrombolysis alone, HBOT sequential or HBOT parallel with thrombolysis. HBOT (2.4 ATA, 1 h) started 45 min (sequential) or 120 min (parallel) after stroke. rtPA was given intravenously 120 min after stroke onset. Functional tests were performed after stroke induction and after treatment. After 6 h infarct volume and intracerebral hemorrhagic complications were assessed.

RESULTS:
Compared to the control group only the combination of HBOT and thrombolysis significantly improved the functional outcome (p=0.03) and reduced the infarct volume (p=0.01), whereas thrombolysis alone did not show a significant benefit. In all treatment groups there was a trend towards fewer hemorrhagic transformations.

CONCLUSION:
Hyperbaric oxygen in combination with thrombolysis shows neuroprotection in acute ischemic stroke in rats by reducing infarct volume and improving functional outcome in the early poststroke period.