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Number 85

# Hyperbaric Oxygen Therapy for Brain Injury, Cerebral Palsy, and Stroke

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**Prepared by:**
Oregon Health & Science University Evidence-based Practice Center
Portland, Oregon

Marian S. McDonagh, PharmD, *Principal Investigator*
Susan Carson, MPH
Joan S. Ash, MLS, MBA, PhD
Barry S. Russman, MD
P. Zoë Stavri, PhD
Kathryn Pyle Krages, AMLS, MA
Mark Helfand, MD, MS, *EPC Director*

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# Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

Carolyn Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Acting Director, Center for Practice and Technology Assessment
Agency for Healthcare Research and Quality

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# Structured Abstract

**Objectives.** The purpose of this report is to describe the methods, results, and conclusions of a literature review of the benefits and harms of hyperbaric oxygen therapy (HBOT) for brain injury, cerebral palsy, and stroke.

**Search Strategy.** We searched MEDLINE, PreMEDLINE, EMBASE, CINAHL, the Cochrane Library, the Health Technology Assessment Database, HealthSTAR, AltHealthWatch and MANTIS from inception to March 2001, using terms for hyperbaric oxygen therapy, brain injury, cerebral palsy, and stroke. We also searched additional databases recommended by experts, meeting abstracts, conference proceedings, and reference lists. Peer reviewers and reference lists of included studies were queried for additional studies. The search was updated in February 2002, and July 2003.

**Selection Criteria.** Two reviewers independently assessed each title and abstract using predetermined inclusion criteria based on intervention, population, outcome measures, and study design criteria. Full papers, reports, and meeting abstracts that met inclusion criteria were retrieved and reviewed independently by two reviewers.

**Data Collection and Analysis.** Extraction of data from studies was performed by one reviewer and checked by a second reviewer. Each study was assessed for quality using predetermined criteria. An overall assessment of each body of literature was made based on the internal and external validity, and consistency and coherence of the results of studies.

**Main Results.** For traumatic brain injury, the evidence about effectiveness is conflicting. One trial found a significant decrease in mortality, associated with an increase in severe disability among those who survived. The other found no difference overall, but a significant reduction in mortality in one subgroup. Together, these studies provided insufficient evidence to determine whether the benefits of HBOT outweigh the potential harms. For other types of brain injury, no good- or fair-quality studies were found. For cerebral palsy, the results of the only truly randomized trial were difficult to interpret because of the use of pressurized room air in the control group. Patients who received HBOT and those who received pressurized air improved to a similar degree. No controlled trial of HBOT was designed to measure mortality in stroke patients, and the best studies found no improvement in neurological outcomes. Evidence about the type, frequency, and severity of adverse events in actual practice is inadequate. Reporting of adverse effects was limited, and no study was designed specifically to assess adverse effects.

**Conclusions.** Evidence from well-conducted clinical studies is limited. The balance of benefits and harms of HBOT for brain injury, cerebral palsy, or stroke has not been adequately studied. Future research of HBOT should include dose-ranging and safety studies to establish the optimum course of HBOT to evaluate in outcome studies. Future clinical trials should include several treatment options and should evaluate measure caregiver burden in addition to patients' functional outcomes.

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Summary

## Overview

Hyperbaric oxygen therapy (HBOT) is the inhalation of 100 percent oxygen inside a hyperbaric chamber that is pressurized to greater than 1 atmosphere (atm). HBOT causes both mechanical and physiologic effects by inducing a state of increased pressure and hyperoxia. HBOT is typically administered at 1 to 3 atm. While the duration of an HBOT session is typically 90 to 120 minutes, the duration, frequency, and cumulative number of sessions have not been standardized.

HBOT is administered in two primary ways, using a monoplace chamber or a multiplace chamber. The monoplace chamber is the less-costly option for initial setup and operation but provides less opportunity for patient interaction while in the chamber. Multiplace chambers allow medical personnel to work in the chamber and care for acute patients to some extent. The entire multiplace chamber is pressurized, so medical personnel may require a controlled decompression, depending on how long they were exposed to the hyperbaric air environment.

The purpose of this report is to provide a guide to the strengths and limitations of the evidence about the use of HBOT to treat patients who have brain injury, cerebral palsy, and stroke. Brain injury can be caused by an external physical force (also known as traumatic brain injury, or TBI); rapid acceleration or deceleration of the head; bleeding within or around the brain; lack of sufficient oxygen to the brain; or toxic substances passing through the blood-brain barrier. Brain injury results in temporary or permanent impairment of cognitive, emotional, and/or physical functioning. Cerebral palsy refers to a motor deficit that usually manifests itself by 2 years of age and is secondary to an abnormality of at least the part of the brain that relates to motor function. Stroke refers to a sudden interruption of the blood supply to the brain, usually caused by a blocked artery or a ruptured blood vessel, leading to an interruption of homeostasis of cells, and symptoms such as loss of speech and loss of motor function.

While these conditions have different etiologies, prognostic factors, and outcomes, they also have important similarities. Each condition represents a broad spectrum, from barely perceptible or mild disabilities to devastating ones. All three are characterized by acute and chronic phases and by changes over time in the type and degree of disability. Another similarity is that the outcome of conventional treatment is often unsatisfactory. For brain injury in particular, there is a strong sense that conventional treatment has made little impact on outcomes.

Predicting the outcome of brain injury, cerebral palsy, and stroke is difficult. Prognostic instruments, such as the Glasgow Coma Scale (GCS) for brain injury, are not precise enough to reliably predict an individual patient's mortality and long-term functional status. Various prognostic criteria for the cerebral palsy patient's function have been developed over the years. For example, if a patient is not sitting independently when placed by age 2, then one can predict with approximately 95 percent confidence that he/she never will be able to walk. However, it is not possible to predict precisely when an individual patient is likely to acquire a particular ability, such

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as smiling, recognizing other individuals, or saying or understanding a new word.

Mortality and morbidity from a stroke are related to older age, history of myocardial infarction, cardiac arrhythmias, diabetes mellitus, and the number of stroke deficits. Functional recovery is dependent on numerous variables, including age, neurologic deficit, comorbidities, psychosocial factors, educational level, vocational status, and characteristics of the stroke survivor's environment.

The report focuses on the quality and consistency of studies reporting clinical outcomes of the use of HBOT in humans who have brain injury, cerebral palsy, or stroke. This information can be used to help providers counsel patients who use this therapy and to identify future research needs.

## Reporting the Evidence

This review addresses the following questions:

1. Does HBOT improve mortality and morbidity in patients who have traumatic brain injury or nontraumatic brain injury, such as anoxic ischemic encephalopathy?
2. Does HBOT improve functional outcomes in patients who have cerebral palsy? (Examples of improved functional outcomes are decreased spasticity, improved speech, increased alertness, increased cognitive abilities, and improved visual functioning.)
3. Does HBOT improve mortality and morbidity in patients who have suffered a stroke?
4. What are the adverse effects of using HBOT in these conditions?

To identify the patient groups, interventions, and outcomes that should be included in the review, we read background material from diverse sources including textbooks, government reports, proceedings of scientific meetings, and Web sites. We also conducted focus groups and interviews to improve our understanding of the clinical logic underlying the rationale for the use of HBOT. In the focus groups, we identified outcomes of treatment with HBOT that are important to patients, caregivers, and clinicians and examined whether patients, caregivers, and clinicians who have experience with HBOT value certain outcomes differently from those who have not used HBOT. A broader goal of the focus groups was to better understand the disagreement between supporters and non-supporters of HBOT.

The following interventions, populations, outcomes, and study design criteria were used to formulate the literature search strategy and to assess eligibility of studies.

- **Intervention.** Hyperbaric oxygen therapy: any treatment using 100 percent oxygen supplied to a patient inside a hyperbaric chamber that is pressurized to greater than 1 atm.
- **Population**. Patients with:
  - brain injury from any cause and in any stage (acute, subacute, or chronic).
  - cerebral palsy of any etiology.
  - thrombotic stroke.
- **Outcomes.** We sought articles reporting any clinical endpoint. We focused on health outcomes, including mortality and functional changes that a patient would experience, rather than intermediate outcomes. Intermediate outcomes include physiologic measures, such as intracranial pressure, cerebrospinal fluid lactate levels, or changes in cerebral blood flow, or results of imaging studies. Some clinical measures, such as neuropsychiatric and cognitive tests, are also intermediate measures. We did not assume that any of these intermediate measures of the effect of HBOT on patients with brain injury, cerebral palsy, or stroke was proven to be an indicator of the long-term outcome. Instead, in reviewing articles for inclusion in this report, we were particularly interested in studies that reported both intermediate measures and health outcomes, to assess the strength of evidence about their correlation.
- **Design.** We included original studies of human subjects that reported original data (no reviews). All study designs except for case reports and small case series were eligible for inclusion. Before-after or time-series studies with no independent control group were included if a) five or more cases were reported, and b) outcome measures were reported for both the pre- and post-HBOT period.

## Methodology

### Technical Expert Advisory Group (TEAG)

We identified technical experts to assist us in formulating the research questions and identifying relevant databases for the literature search. The expert panelists included a neurologist specializing in stroke, a neurosurgeon specializing in severe brain injury, a pediatric neurologist with expertise in treating patients with cerebral palsy, and a physician with an HBOT practice. Throughout the project period, we consulted individual members of the TEAG on issues that arose in the course of identifying and reviewing the literature.

### Literature Search, Study Selection, and Data Extraction

We searched a broad range of databases to identify published and unpublished studies of the effectiveness and harms of HBOT in patients with brain injury, cerebral palsy, and stroke. Each database was searched from its starting date to March 2001. The databases searched were:

- MEDLINE®
- PreMEDLINE®

- EMBASE
- HealthSTAR (Health Service Technology, Administration and Research)
- CINAHL® (Cumulative Index to Nursing & Allied Health)
- Cochrane Database of Systematic Reviews
- Cochrane Controlled Trials Register
- DARE (Database of Abstracts of Reviews of Effectiveness)
- AltHealthWatch
- MANTIS™ (Manual, Alternative and Natural Therapy)
- Health Technology Assessment Database

TEAG members identified the following additional databases as potential sources of other material that may not be indexed in other electronic databases:

- The Undersea & Hyperbaric Medical Society: a large bibliographic database
- The Database of Randomised Controlled Trials In Hyperbaric Medicine
- European Underwater and Baromedical Society
- International Congress on Hyperbaric Medicine
- National Baromedical Services, Inc.

Update literature searching of the electronic databases MEDLINE, PreMEDLINE, EMBASE, CINAHL, the Cochrane Library, and the Health Technology Assessment Database was completed on February 26, 2002, using the same search strategy as used for the initial searches. Eight additional references submitted by a peer reviewer were added in May 2003. Finally, a supplemental search of MEDLINE, PreMEDLINE, EMBASE, and CINAHL was conducted in July 2003.

The references of all included papers were hand searched. In addition, two reviewers independently conducted hand searches of the references from the *Textbook of Hyperbaric Medicine*.[1] One TEAG member provided articles and meeting abstracts from his personal library.

Two reviewers independently assessed each title and abstract located through the literature searches for relevance to the review, based on the intervention, population, outcome, and study design criteria. The full-text articles, reports, or meeting abstracts that met the criteria listed above were retrieved and reviewed independently by two reviewers who reapplied the eligibility criteria. Disagreements were resolved through consensus.

Extraction of data from studies was performed by one reviewer and checked by a second reviewer. Disagreements were resolved through consensus.

## Internal and External Validity and Quality Rating

The quality of all trials in the review was assessed using a list of items indicating components of internal validity. We modified the standard checklists to address issues of particular importance in studies of HBOT. For randomized controlled trials (RCTs) and nonrandomized controlled trials (NRCTs), the items assessed for internal validity were: randomization/allocation concealment, baseline comparability of groups, timing of baseline measures, intervention, outcome measures, timing of followup measurements (long enough to assess effects), loss to followup, handling of dropouts or missing data, masking, statistical analysis (if any), and general reviewer comments.

For the observational studies, items assessed for internal validity were exposure measurement (whether all subjects were given the same HBOT treatment), other interventions, differences in baseline factors among the groups of subjects compared (if a comparison group was included), discussion of or control for potential confounding, masking, evidence of stable baseline, timing of baseline survey, timing of followup measures, outcome measures used, and general comments of the reviewer.

Each study was then assigned an overall rating (good, fair or poor) according to the US Preventive Services Task Force method:

- **Good:** Comparable groups assembled initially (adequate randomization and concealment, and potential confounders distributed equally among groups) and maintained throughout the study; followup at least 80 percent; reliable and valid measurement instruments applied equally to the groups; outcome assessment masked; interventions defined clearly; all important outcomes considered; appropriate attention to confounders in analysis; for RCTs, intention-to-treat analysis.
- **Fair:** Generally comparable groups assembled initially (inadequate or unstated randomization and concealment methods) but some question remains whether some (although not major) differences occurred with followup; measurement instruments acceptable (although not the best) and generally applied equally; outcome assessment masked; some, but not all, important outcomes considered; appropriate attention to some, but not all, potential confounders; for RCTs, intention-to-treat analysis.
- **Poor:** Groups assembled initially not close to being comparable or not maintained throughout the study; measurement instruments unreliable or invalid or not

[1] Jain K, editor. Textbook of hyperbaric medicine. 3rd rev. ed. Kirkland, WA: Hogrefe & Huber Publishers, Inc; 1999.

applied equally among groups; outcome assessment not masked; key confounders given little or no attention; for RCTs, no intention-to-treat analysis.

For each study, the reviewer's assessment of external validity is given, including an assessment of the evidence that the study population reflects the underlying patient population (age-range, co-morbidities, co-interventions, etc.). External validity indicates the applicability of the results of the study to clinical practice. For example, if the study recruited a narrowly defined group of patients, the results may not be generalizable to a broader spectrum of patients. A study can have high internal validity but low external validity. There are no well-defined criteria for assessing external validity, and clinicians must assess the applicability of the results to the patient population for which the intervention is intended.

## Findings

### Brain Injury

- For traumatic brain injury, one randomized trial provided fair evidence that HBOT might reduce mortality or the duration of coma in severely injured TBI (traumatic brain injuries) patients. However, in this trial, HBOT also increased the chance of a poor functional outcome. A second fair quality randomized trial found no difference in mortality or morbidity overall, but a significant reduction in mortality in one subgroup. Therefore, they provide insufficient evidence to determine whether the benefits of HBOT outweigh the potential harms.
- The quality of the controlled trials was fair, meaning that deficiencies in the design add to uncertainty about the validity of results.
- Due to flaws in design or small size, the observational studies of HBOT in TBI do not establish a clear, consistent relationship between physiologic changes after HBOT sessions and measures of clinical improvement.
- The evidence for use of HBOT in other types of brain injury is inconclusive. No good- or fair-quality studies were found.

### Cerebral Palsy

- There is insufficient evidence to determine whether the use of HBOT improves functional outcomes in children with cerebral palsy. The results of the only truly randomized trial were difficult to interpret because of the use of pressurized room air in the control group. As both groups improved, the benefit of pressurized air and of HBOT at 1.3 to 1.5 atm should both be examined in future studies.
- The only other controlled study compared HBOT treatments with 1.5 atm to delaying treatment for 6 months. As in the placebo-controlled study, significant improvements were seen, but there was not a significant difference between groups.
- Two fair-quality uncontrolled studies (one time-series, one before-after) found improvements in functional status comparable to the degree of improvement seen in both groups in the controlled trial.
- Although none of the studies adequately measured caregiver burden, study participants often noted meaningful reductions in caregiver burden as an outcome of treatment.

### Stroke

- Although a large number of studies address HBOT for the treatment of stroke, the evidence is insufficient to determine whether HBOT reduces mortality in any subgroup of stroke patients because no controlled trial assessed was designed to assess mortality.
- Among controlled trials, the evidence about morbidity is conflicting. The three best-quality trials found no difference in neurological measures in patients treated with HBOT versus patients treated with pressurized room air.
- Two other controlled trials, one randomized and one nonrandomized, found that HBOT improved neurological outcomes on some measures. However, both were rated poor-quality.
- Most observational studies reported favorable, and sometimes dramatic, results, but failed to prove that these results can be attributed to HBOT. For example, one retrospective study found better mortality rates in patients who received HBOT than a comparison group of patients from a different hospital who did not. The study did not provide information on mortality rates from other causes in each hospital; this information would have made it easier to judge whether the improved survival was due to HBOT or to differences in overall quality of care at the HBOT hospital.
- The observational studies of HBOT provided insufficient evidence to establish a clear relationship between physiologic changes after HBOT sessions and measures of clinical improvement. Few studies established that patients were stable at baseline.

### Adverse Events

- Evidence about the type, frequency, and severity of adverse events in actual practice is inadequate. Reporting of adverse effects was limited, and no study was designed specifically to assess adverse effects.
- The few data that are available from controlled trials and cohort studies of TBI suggest that the risk of seizure may be higher in patients with brain injuries treated with HBOT.

- No study of HBOT for brain injury, cerebral palsy, or stroke has been designed to identify the chronic neurologic complications.
- Pulmonary complications were relatively common in the trials of brain-injured patients. There are no reliable data on the incidence of aspiration in children treated for cerebral palsy with hyperbaric oxygen.
- Ear problems are a known potential adverse effect of HBOT. While ear problems were reported in brain injury, cerebral palsy, and stroke studies the incidence, severity and effect on outcome are not clear. However, the rates reported among cerebral palsy patients were higher (up to 47 percent experiencing a problem) than reported with brain injury or stroke. However, the data in brain injury are limited by the use of prophylactic myringotomies.

### Supplemental Qualitative Analysis

- Opinions about the frequency and severity of risks of HBOT vary widely.
- Several participants emphasized the importance of continued treatments to maximize results.
- Patients and caregivers value any degree of benefit from HBOT highly. An improvement that may appear small on a standard measure of motor, language, or cognitive function can have a very large impact on caregiver burden and quality of life.

## Future Research

### Outcome Studies

We identified several barriers to conducting controlled clinical trials of HBOT for brain injury, particularly cerebral palsy:

- Lack of agreement on the dosage and the duration of treatment.
- Need for better measures of relevant outcome measures, such as caregiver burden.
- Lack of independent, reliable data on the frequency and severity of adverse events.
- Patients' unwillingness to be assigned to a placebo or sham treatment group.

As described below, strategies can be developed to conduct good-quality studies to overcome each of these barriers.

**Dose and duration of treatment.** Oxygen, the "active ingredient" in HBOT, is fundamentally a drug. As for any drug, dose and duration of treatment must be determined in carefully designed dose-ranging studies before definitive studies demonstrating clinical efficacy can be started. Good-quality dose-ranging studies of HBOT for brain injury can be done, based on the model used by pharmaceutical manufacturers and the FDA. It is likely that the dosage of HBOT needs to be individualized based on the patient's age, clinical condition, and other factors. This is the case for many other drugs and does not pose an insurmountable barrier to designing dose-finding trials. In fact, the need to individualize therapy makes it essential to base the design of long-term studies of clinical outcomes on the results of dose-ranging studies.

**Better outcome measures.** In describing the course of their patients, experienced clinicians who use HBOT to treat patients with brain injury, cerebral palsy, and stroke refer to improvements that may be ignored in standardized measures of motor and neuro-cognitive dysfunction. These measures do not seem to capture the impact of the changes that clinicians and parents perceive. Caregivers' perceptions should be given more weight in evaluating the significance of objective improvements in a patient's function. Unfortunately, studies have not consistently measured caregiver burden, or have assessed it only by self-report. Studies in which the caregivers' burden was directly observed would provide much stronger evidence than is currently available about treatment outcome.

**Adverse events.** Uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT. The case against HBOT is based on the reasoning that, because HBOT may be harmful, it must be held to the highest standard of proof. A corollary is that, if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its efficacy can be lowered.

Good-quality studies of adverse effects are designed to assess harms that may not be known or even suspected. The most common strategy is to use a standard template of several dozen potential adverse effects affecting each organ system. Other characteristics of a good study of adverse events are a clear description of patient selection factors, independent assessment of events by a neutral observer, and the use of measures for the severity (rather than just the occurrence) of each event.

**Unwillingness to be in a placebo group.** The issue of placebo groups has been the subject of a great deal of debate. Participants on both sides make the assumption that an "evidence-based" approach implies devotion to double blind, placebo-controlled trials without regard to practical or ethical considerations. This assumption is false. Double blind, placebo-controlled trials are the "gold standard" for government regulators overseeing the approval of new pharmaceuticals, but not for clinical decision making or for insurance coverage decisions. Evidence-based clinical decisions rely more heavily on comparisons of a treatment to other potentially effective therapies than to placebos.

Several alternatives to the double blind, placebo-controlled trial can be used to examine effectiveness. One approach is to compare immediate to delayed treatment with HBOT, as was done in the Cornell trial. Another is to design a trial in which patients are randomly assigned to several alternative HBOT regimens. Because of uncertainty about the dosage and

duration of treatment, such a trial would be preferable to a trial that offered a choice between one particular regimen and no treatment at all. It is also easier to incorporate a sham therapy arm in such a trial: patients may be more willing to enter a trial if they have a 10 percent or 20 percent chance of being assigned to sham treatment instead of a 50 percent chance. Other alternatives to a placebo include conventional physical, occupational, and recreational therapy, or another alternative therapy, such as patterning.

The Canadian trial of HBOT for cerebral palsy has important implications for the design of future research. In the trial there was a clinically significant benefit in the control group. Debate about the trial centers largely on how the response in the control group should be interpreted. The trial investigators believe that the beneficial effect was the result of the psychological effect of participating in the trial and extra attention paid the children in and out of the hyperbaric chamber. Alternatively, the slightly pressurized air (that is, "mild" hyperbaric oxygen) may have caused the improvement. A third possibility is that the slightly increased oxygen concentration, not the pressure per se, was responsible for the benefit.

A trial that could sort out which of these explanations was true would have a major impact on clinical practice. Such a trial might compare (1) room air under slightly elevated pressure, delivered in a hyperbaric chamber, to (2) elevated oxygen concentration alone, delivered in a hyperbaric chamber, and to (3) an equal amount of time in a hyperbaric chamber, with room air at atmospheric pressure. From the perspective of a neutral observer, the third group is not a "sham" but rather an attempt to isolate the effect of the social and psychological intervention cited by the Canadian investigators.

In addition to needing improved design, future trials of HBOT need better reporting. This would aid interpretation and the application of the research results. Two types of information are essential: a clear description of the research design, particularly of the control and comparison groups, and a detailed description of the patient sample. It is frequently difficult to tell from published studies how comparable the patient populations are, not only demographically but also clinically, in order to interpret the diagnosis and prognosis.

## Studies of Diagnosis and Nonclinical Endpoints

An independent, critical assessment of the body of animal experiments and human case studies supporting the "idling neuron" theory of brain injury and recovery should have been done. A large body of studies supports the theory underlying the use of HBOT, but the interpretation of these studies is also disputed. Most of these studies use experimental animal models of brain injury and are designed to provide support for the hypothesis that HBOT redirects blood flow to, and promotes recovery and growth of, "idling neurons" at the border of the damaged brain tissue.

There is sharp disagreement in the medical literature over the validity of these experimental models. One major issue is the significance of improvements in patterns of cerebral blood flow. The principle that redirecting flow toward ischemic areas can help damaged tissue recover is well established in cardiology. However, in critical care generally, drugs and maneuvers that redirect flow to ischemic organs (e.g., brain and kidney) do not always improve recovery at the cellular level. For this reason, improved blood flow must be linked to other measures of cellular and organ recovery.

HBOT for brain injury is not likely to gain acceptance in routine clinical use until a clinical method of assessing its effectiveness in the individual patient is validated.Specifically, the diagnostic value of SPECT scans and of other intermediate indicators of the effects of HBOT should be examined in good-quality studies. Like all other diagnostic tests, SPECT scans have a measurable false positive and false negative rate in relation to clinical outcomes. Controlled trials are not needed as the ideal study design to measure the accuracy of a diagnostic test. Rather, a longitudinal cohort study in which all patients undergo scans as well as standardized followup tests would be a feasible and ideal approach.

## Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Oregon Health & Science University Evidence-based Practice Center, under Contract No. 290-97-0018. It is expected to be available in September 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 85, *Hyperbaric Oxygen Therapy for Brain Injury, Cerebral Palsy, and Stroke,* (AHRQ Publication No. 04-E003). In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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# Evidence Report

# Chapter 1. Introduction

## Purpose

This evidence report describes the methods, results, and conclusions of a literature review on the use of hyperbaric oxygen therapy (HBOT) to treat manifestations of brain injury, cerebral palsy, and stroke in humans. Hyperbaric oxygen therapy is the administration of high concentrations of oxygen within a pressurized chamber. HBOT has become the definitive therapy for patients with decompression illness, gas embolism, and severe, acute carbon monoxide poisoning and is a widely accepted treatment for osteoradionecrosis, soft tissue radionecrosis, wound healing, and several other conditions. However, the role of HBOT in the treatment of patients with brain injuries is controversial.

*Brain injury* can be caused by an external physical force (this is also known as traumatic brain injury, or TBI); rapid acceleration or deceleration of the head; bleeding within or around the brain; lack of sufficient oxygen to the brain; or toxic substances passing through the blood-brain barrier. A brain injury results in a temporary or permanent impairment of cognitive, emotional, and/or physical functioning. *Cerebral palsy* refers to a motor deficit that usually manifests itself by 2 years of age and is secondary to an abnormality of at least the part of the brain that relates to motor function. *Stroke* refers to a sudden interruption of the blood supply to the brain, usually caused by a blocked artery or a ruptured blood vessel, leading to an interruption of homeostasis of cells, and symptoms such as loss of speech and loss of motor function.

While these conditions have different etiologies, prognostic factors, and outcomes, they also have important similarities. Each condition represents a broad spectrum, from barely perceptible or mild disabilities to devastating ones. All three are characterized by acute and chronic phases and by changes over time in the type and degree of disability. Another similarity is that, for all three conditions, the outcome of conventional treatment is often unsatisfactory. For brain injury in particular there is a strong sense that conventional treatment has had little impact on outcomes.[1] The use of various diagnostic and therapeutic interventions including pre-hospital intubation, intracranial pressure monitoring, intracranial pressure-directed therapy, and head computed tomography scan utilization vary considerably among different centers.[2] Such variation often signifies a lack of consensus on clinical effectiveness.

In early 2000, the Agency for Healthcare Research and Quality asked the Oregon Evidence-based Practice Center to assess the feasibility of conducting a full evidence report on the use of HBOT for treatment of brain injury and stroke. In response, in March 2001, the Oregon EPC conducted a literature search to identify clinical studies of the use of HBOT for chronic stroke and other brain injury. The EPC found that there are controlled studies of at least fair internal and external validity that measured at least some relevant outcomes of HBOT for each type of brain injury. The EPC recommended that a full evidence report be done to provide insight into what is currently known and not known about the efficacy of HBOT in these conditions and shed light on what is missing from the current evidence base. The EPC also recommended that the evidence report should include an assessment of what outcomes are important to patients, caregivers, and clinicians.

After reviewing the results of the feasibility study, AHRQ asked the Oregon EPC to prepare a full evidence report. The purpose of this evidence report is to assess the strength of the evidence about the benefits and risks of HBOT for brain injury, cerebral palsy, and stroke.

# Background

## Traumatic Brain Injury

Each year, approximately 1.5 million Americans sustain traumatic brain injuries, ranging in severity from mild to fatal.[3, 4] The leading causes of traumatic brain injury are motor vehicle crashes, falls, firearm use, and sports and recreational activities. Adolescents and young adults (aged 15 to 24) as well as adults aged 65 years and older have the highest risk. The annual costs of traumatic brain injuries are estimated to be $56 billion.[5] This figure reflects the costs of medical care and rehabilitation as well as the loss of productivity and income among individuals who have long-term disability due to their injuries.

Of the 1.5 million who are injured each year, 50,000 die, and from 80,000 to 90,000 experience the onset of long-term disability.[3] The Centers for Disease Control has estimated that 5.3 million Americans are living with disability as a result of brain injury. The types of disability range across the entire spectrum of human physical, social, and emotional function. No single instrument can measure all of the consequences of TBI. The two most commonly used measures of outcome were developed for use with severe brain injury. The oldest formal scale, the Glasgow Outcome Scale (GOS), categorizes patients into five broad categories: good recovery, moderate disability, severe disability, persistent vegetative state, and death.[6] This measure is convenient and very widely used, but it is insensitive to many of the cognitive and emotional deficits that, while subtle, have a strong effect on quality of life.

Another commonly used instrument is the Disability Rating Scale (DRS), a 30-point scale based on ratings of the level of consciousness or arousal, cognitive ability for self-care, physical dependence on others, and ability to work.[7] Other measurement instruments have been designed to assess subtler degrees of disability in memory, cognition, attention, social function, or emotional function in chronic brain injury patients. These measures include the Community Integration Questionnaire, the Neurobehavioral Functioning Inventory (NFI), the Patient Competency Rating Scale (PCRS), the Level of Cognitive Functioning Scale (LCFS), and the Revised Craig Handicap Assessment and Reporting Technique (R-CHART).

The prognosis of TBI is related to the severity of the initial injury. Since the 1970s, the Glasgow Coma Scale (GCS) (Table 1) has been the most widely used measure of the severity of an acute brain injury.[8, 9] The scores range from 3 to 15. Three to five is the most serious, and 13 to15 is the mildest, with the best prognosis. "Severe" injury is often defined as a GCS score of 8 or less. For patients with TBI, a score in this range indicates a mortality rate of 50 percent and a high likelihood of suffering from severe long-term disabilities.[10-13]

GCS has several limitations as a predictor for an individual's outcome. Data about the ability of GCS scores to predict functional outcomes come from patients who undergo inpatient rehabilitation, rather than from all patients who are seen for trauma.[14] Patients excluded from inpatient rehabilitation because they are not as severely impaired, are too impaired to benefit, or lack financial resources, have not been well studied. In trauma patients, mortality rates differ between different groups of patients who have similar average GCS scores. For a given GCS score, survival also varies considerably among published studies.[15] The inter-observer reliability of the GCS is only fair, and the differences between observers are large enough to alter the predicted prognosis substantially.[16] Patients who have the same total GCS score, but different scores on the components of the GCS, have different mortality rates.[17]

**Table 1. Glasgow Coma Scale**

**Eye Opening Response**

- Spontaneous--open with blinking at baseline **4 points**
- To verbal stimuli, command, speech **3 points**
- To pain only (not applied to face) **2 points**
- No response **1 point**

**Verbal Response**

- Oriented **5 points**
- Confused conversation, but able to answer questions **4 points**
- Inappropriate words **3 points**
- Incomprehensible speech **2 points**
- No response **1 point**

**Motor Response**

- Obeys commands for movement **6 points**
- Purposeful movement to painful stimulus **5 points**
- Withdraws in response to pain **4 points**
- Flexion in response to pain (decorticate posturing) **3 points**
- Extension response in response to pain (decerebrate posturing) **2 points**
- No response **1 point**

In addition to GCS, factors such as age,[15, 18, 19] associated injuries,[20] intracranial hypertension,[21, 22] and the presence of a mass effect[23] are also predictors of mortality and severe disability. Preinjury productivity and education also help predict functional outcome in survivors.[24, 25] Hypoxia (defined as PaO2 less than 60 mm Hg, or apnea or cyanosis in the field) and hypotension (defined as a measure of systolic blood pressure less than 90 mm Hg at any time) are also strong predictors of death and severe disability.[22, 26-28]

Some features of the patient's course and management in the hospital are also predictors of mortality and morbidity. For example, the extent of post-traumatic amnesia (PTA) is correlated with the prognosis. The longer the amnesia occurs following the injury, the worse the prognosis for recovery. If the loss of consciousness lasts more than 4 weeks, a high prevalence of impairment, inattention, and memory loss is predicted.[29]

During the course of intensive care, episodes of hypotension, elevated intracranial pressure, decreased cerebral perfusion, and hypoxia are also predictors of a poor outcome.[30] Such episodes are very common. In a series of 184 patients receiving intensive care for acute, severe TBI,[30] all but seven patients had at least one episode of hypotension. In 157 of these patients, jugular venous oxygen saturation was monitored continuously. Ninety-seven (62 percent) of these patients experienced one or more episodes of hypoxia (jugular venous oxygen saturation <50 percent), and patients spent an average of 1.88 hours in a hypoxic state during the intensive care unit stay. These figures probably represent better-than-typical results because they were obtained in an intensive care unit that used invasive monitoring to minimize the frequency and duration of hypoxic episodes.

GCS and other prognostic factors are of little value in predicting the speed of recovery from coma. In before-after comparison studies, a presumption is often made that a patient who was discharged from the acute care hospital in a vegetative state has a very low chance of recovering consciousness spontaneously. However, several cases of recovery have been documented in

patients who have had stable coma for longer than 6 months.[31] In case series of patients with severe or catastrophic traumatic brain injuries, three of four patients who survived 6 months regained consciousness.[18]

Similarly, data from recent followup studies contradict the widely held view that improvements in neurocognitive function are unlikely to occur if more than a year has passed since the injury.[32, 33] In one of these cohort studies, patients with TBI were administered a battery of 12 neuropsychological tests 1 year and 5 years after injury.[33] On one of the tests (Trails B, a test of complex attention), 22.2 percent of patients improved and 14.1 percent deteriorated between 1 and 5 years post-injury. For the other 11 tests, 0 to 22.7 percent (median 13 percent) improved and 1.2 percent to 18 percent (median 6.2 percent) deteriorated. The authors concluded that clinically significant improvements can occur long after apparently "stable" deficits have been diagnosed.

Nearly 90 percent of TBIs that are reported annually in the United States are classified as mild TBI (MTBI) or concussion. MTBI can cause immediate neurocognitive abnormalities[34] as well as long-term problems such as persistent headaches, confusion, memory problems, mood changes, and changes in vision or hearing.[35] The incidence of MTBI may be under-reported because a large percentage of patients never seek medical evaluation or treatment. Moreover, the subtle long-term consequences of MTBI, although often apparent to patients and family members, may go unrecognized by physicians. It is difficult to predict which patients with MTBI will suffer long-term disability.

Many components of acute and rehabilitative care for patients with brain injuries are not supported by good-quality evidence from clinical trials.[27, 36, 37] A recent consensus conference on clinical trials in head injury summarized the disappointing results of over a dozen treatments which despite promising results in observational studies, proved to be ineffective when tested in randomized trials.[38] Most of these treatments appeared to be effective in animal studies, case reports, and other before-after studies.

Cerebral perfusion pressure (CPP) management provides the best example. Following several case reports and small series, Rosner and colleagues published a series of 158 patients admitted with a Glasgow Coma Scale score less than 7 who underwent cerebral perfusion pressure (CPP) management rather than the conventional approach, control of intracranial pressure (ICP).[39] Mortality was only 29 percent, and 59 percent achieved a good recovery or moderate disability by 6 months post-injury. The authors stated that these mortality and recovery rates were much better than would be expected from other series of patients who had similar GCS scores. These results led to wide use of the CPP management strategy. However, in a subsequent randomized controlled trial that recruited patients with a GCS score less than 5, mortality was under 30 percent in both the cerebral blood flow-targeted and conventionally managed groups, and there was no difference in neurologic outcomes.[40] In this trial, the cerebral blood-flow-targeted strategy significantly reduced the frequency of cerebral ischemia and of jugular desaturation, but these physiologic improvements did not translate into clinical benefits.

Hypothermia provides a similar example. In the 1990s, several groups of investigators published dramatic case studies and series of cases that appeared to show that inducing hypothermia in brain-injured patients improved outcomes.[41-43] The goal of this treatment was to reduce hypoxia in the injured brain tissue. In one series, the investigators used hypothermia in 148 patients who had initial GCS scores less than 6.[41] Mortality was 30 percent, and, as measured by the Glasgow Outcome Scale, 40 percent of patients had a good recovery, 13 percent had mild disability, and 10 percent were in a persistent vegetative state. Subsequently, in a

randomized trial of 392 patients, mortality was 28 percent in the hypothermia group and 27 percent in the normothermia group. An additional 30 percent of patients in each group had severe disability or a vegetative state. The hypothermia group had fewer episodes of high intracranial pressure but also had more hospital days because of complications.

These examples show that improvements in physiologic measures do not always translate into tangible clinical results. They also show that relying on assumptions about the expected prognosis of a group of brain-injured patients, rather than on results in a control group, can be misleading.[1] Even over a short time there can be significant changes in the prognosis of TBI. In one trauma center, for example, mortality among patients with a GCS ≥ 4 fell from 40 percent in the period 1980-1981 to 27 percent in 1987-1988 and 2.8 percent in 1996-1997.[44]

## Anoxic-ischemic Brain Injury

It is estimated that, in the U.S., more than 1,000 useful lives are lost each day as a result of poor cardiopulmonary and trauma resuscitation outcomes.[45] Among those who survive, permanent brain injury is a common, devastating complication. In addition to cardiopulmonary arrest, toxic substances, congenital disorders, and birth trauma can cause brain injury by means of anoxia and ischemia.

Prediction of the outcome of coma due to anoxic-ischemic coma is poor. In a meta-analysis of studies of patients with anoxic-ischemic coma, the sensitivity of a GCS score of 3 to 5 ranged from 63 percent to 95 percent for a poor outcome, defined as death or persistent vegetative state.[46] The specificity of a GCS in this range was 54 percent to 100 percent. The meta-analysis found that clinical variables are less accurate in predicting outcome after 24-hour coma duration than after 72 hours of coma. The most specific predictors of outcome were the lack of pupillary light reflexes after 72 hours, lack of motor response to pain after 72 hours, and certain somatosensory evoked potential findings. A subsequent meta-analysis by the same authors found there was insufficient evidence to determine whether markers of central nervous system metabolism added substantially to the predictive value of these variables.[47]

## Cerebral Palsy

Each year, about 10,000 babies born in the U.S. develop cerebral palsy. More than 500,000 Americans have cerebral palsy. A study in California showed that the lifetime costs per new case of cerebral palsy was $503,000 (in 1992 dollars).[48] Half of these costs are borne by families, who often find it difficult to obtain all the services they need to help their children.

Cerebral palsy results from injury to the brain. About 20 percent of children who have cerebral palsy acquire the disorder after birth, while 80 percent of cases are congenital. Meningitis, encephalitis, and trauma cause most of the acquired cases. According to the National Institute of Neurological Disorders and Stroke, the mechanism of injury in the majority of cases of congenital cerebral palsy is not known. Until recently, the belief that birth complications cause most cases of cerebral palsy was widespread. Then, in the 1980s, a careful study of 35,000 births showed that fewer than 10 percent of children with cerebral palsy had a history of birth complications such as rubella or other infections during pregnancy, jaundice, Rh incompatibility, asphyxia (oxygen shortage), or head trauma during labor and delivery. Most children with congenital cerebral palsy do not have a history of any of these conditions.

Premature birth and low birthweight predispose to cerebral palsy, but the reason for this association is not clear.

Cerebral palsy represents a very broad range of motor disorders, varying in the part of the body they affect (e.g., diplegia, hemiplegia, quadriplegia); the type of motor disorder (spastic, athetoid, or ataxic) and their severity. The most familiar pattern is spastic diplegia, meaning that the patient has stiff, contracted muscles in the legs. By definition, the muscle disorder in cerebral palsy is not progressive. However, muscle spasticity, even if stable, can cause new problems as a child grows. For example, pain and contractures may increase as the bones of the child's legs lengthen.

Standardized scales, such as gait analysis, and functional scales, such as the Gross Motor Function Measure (GMFM), are used to assess and monitor progress. The GMFM is a validated and reliable scale used for measuring function in patients with cerebral palsy. It consists of five domains with a possible total score of 88. Various prognostic criteria for the patient's function have been developed over the years. For example, if a patient is not sitting independently when placed by age 2, then one can predict with approximately 95 percent confidence that he/she never will be able to walk.[49] On occasion, such a child will walk, but usually aids are necessary, such as a walker. Most children with cerebral palsy will improve in their function over time, [50] but many have deficits that continue into adulthood.

## Stroke

Mortality and morbidity from a stroke are related to older age, history of myocardial infarction, cardiac arrhythmias, diabetes mellitus, and the number of stroke deficits.[51] Evaluation by magnetic resonance imaging (MRI) of the brain obtained during the first few days of the stroke will predict a favorable outcome if less than 80 cc of the brain is infarcted.[52] The 30-day survival after a first stroke has been estimated to be less than 80 percent.[53] For those who survive, it has been estimated that 95 percent of patients reach maximal recovery within 3 to 5 months of the stroke.[54] Functional recovery is dependent on numerous variables, including age, neurologic deficit, comorbidities, psychosocial factors, educational level, vocational status, and characteristics of the stroke survivor's environment.

## Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is the inhalation of 100 percent oxygen inside a hyperbaric chamber pressurized to greater than 1 atmosphere (atm). HBOT causes both mechanical and physiologic effects by inducing a state of increased pressure and hyperoxia. Hyperbaric oxygen pressure is expressed in multiples of atmospheric pressure at sea level, where 1 atm is about 760 mm Hg or 1 kilogram per square centimeter.[55, 56] The oxygen dissolved in blood at 1 atm (sea level) breathing room air is 0.3 ml/dL, and this is in addition to hemoglobin-bound oxygen. Breathing 100 percent oxygen at 1 atm results in an increase in blood oxygenation to 1.5 ml/dL. Increasing the pressure to 3 atm increases the blood oxygen (dissolved oxygen, not carried by hemoglobin) to 6 ml/dL.[57, 58] At rest and with good perfusion, tissues require 5-6 ml/dL of oxygen, whether from dissolved or hemoglobin-bound oxygen. Hence, in situations where hemoglobin-bound oxygen is limited (e.g., carbon monoxide poisoning), tissue oxygen needs can be met without hemoglobin-carried oxygen.

In addition to this hyperoxic effect, the increased pressure reduces the volume of gases in the blood by virtue of Boyle's law (in an enclosed space, the volume of a gas is inversely

proportionate to the pressure exerted upon it). This is the mechanism relied upon in decompression illness and arterial gas embolism to reduce the size of the gas bubbles and allow replacement of inert gas in the bubbles with oxygen, which can be metabolized by tissues.

HBOT can be administered in two primary ways, using a monoplace chamber or a multiplace chamber.[59, 60] The monoplace chamber serves one patient at a time. It is the less-costly option for initial setup and operation but provides less opportunity for patient intervention while in the chamber. Monoplace chambers are generally constructed of clear acrylic or with acrylic view ports that allow for patient observation. Monoplace chambers are generally pressurized with 100 percent oxygen.

Multiplace chambers allow medical personnel to work in the chamber and care for acute patients to some extent. Each patient is given 100 percent oxygen through a facemask, tight-fitting hood, or endotracheal tube. The entire multiplace chamber is pressurized with air, so medical personnel may require a controlled decompression, depending on how long they are exposed to the hyperbaric air environment.

While the duration of an HBOT session is typically 90 to 120 minutes, the duration, frequency, and cumulative number of sessions has not been standardized. The dose received by the patient may be affected by the type of chamber used. Monoplace chambers using face masks or hoods that do not fit snugly may result in dilution of 100 percent oxygen with room air.[59]

## Indications for HBOT

HBOT is used in a wide range of conditions. The following list indicates those uses that are currently recognized by the Food and Drug Administration (FDA):

1. Air or Gas Embolism
2. Carbon Monoxide Poisoning
3. Clostridal Myositis and Myonecrosis (Gas Gangrene)
4. Crush Injury, Compartment Syndrome, and other Acute Traumatic Ischemias
5. Decompression Sickness
6. Enhancement of Healing in Selected Problem Wounds
7. Exceptional Blood Loss (Anemia)
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections
10. Osteomyelitis (Refractory)
11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
12. Skin Grafts & Flaps (Compromised)
13. Thermal Burns
14. Actinomycosis

This list of FDA-approved indications was based on a list of accepted indications produced by the Undersea and Hyperbaric Medical Society (UHMS) in 1978 and updated by the UHMS in 2002.[61] The Centers for Medicare and Medicaid Services (CMS) has a similar list of indications for which it provides coverage. This list is further delineated by the ICD-9 codes used for these indications. These two additional lists appear in Appendix A. Stroke, brain injury, and cerebral palsy are not currently included on these lists of approved indications.

The CMS recently commissioned a systematic review of the evidence for the effectiveness of HBOT in treating hypoxic wounds.[62, 63] The review found that of the 10 types of wounds

currently covered by CMS, "there is sufficient objective evidence that HBOT aids in wound healing for: compromised skin grafts, osteoradionecrosis, gas gangrene, progressive necrotizing infections, and nonhealing wounds. There was evidence from case series suggesting the beneficial effect of HBOT for soft tissue radionecrosis,"[62] but evidence was insufficient to support its use for acute traumatic peripheral ischemia (one case series), crush injuries and suturing of severed limbs (one randomized controlled trial), acute peripheral arterial insufficiency (no study), and chronic refractory osteomyelitis (one non-randomized study, one case series). In a decision memorandum on August 30, 2002, CMS found adequate evidence to continue to provide coverage for the use of HBOT to treat diabetic lower extremity wounds, but did not extend coverage to hypoxic wounds.[64]

## Current Policy and Regulation of HBOT

Hyperbaric chambers are classified as class II medical devices by the FDA, and as such require the manufacturers to comply with specific regulations before marketing. The regulatory process requires the manufacturer to specify the intended uses of the device. Manufacturers applying for uses beyond the 14 already acknowledged are required to submit supporting evidence. The evidence would be reviewed by the Center for Drug Evaluation and Research (CDER) in consultation with the Center for Devices and Radiological Health (CDRH). An Investigational New Drug Application (IND) would be required for studies of significant risk, and Investigational Review Board (IRB) approval for any study.[65] Manufacturers cannot advertise or promote uses that are not approved by the FDA.

The FDA has deemed hyperbaric chambers to be prescription devices. This designation requires that a valid prescription is required prior to use. Practitioners authorized to prescribe HBOT vary by state. As is the case with other prescription devices and drugs, a physician who believes that HBOT is the best therapy for a patient with an indication that is not on the list may prescribe HBOT for this "off-label" use.

At present, there are no individual state or nationally mandated standards for hyperbaric facility staffing or training. Other local, state, and federal regulations may apply to the chambers, primarily fire safety and building code regulations. Currently, other types of accreditation or certification of chambers and personnel are not strictly required. Third-party reimbursement typically requires that a physician be present during treatments and is limited to the 13 indications approved by the FDA. Medical center-based chambers also must comply with additional safety and quality-of-care criteria as required by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

## Cost of HBOT

In 1996, the cost of an average 90-minute session in the United States was reported to be $300-$400.[56] However, increased demand for HBOT and availability of fee-for-service chambers may have altered the typical cost. A year 2000 report by the Office of the Inspector General[66] reviewed the use of HBOT among Medicare recipients between 1995 and 1998. The average total allowed charge per treatment in 1998 was $405, with an average allowed therapy cost per patient of approximately $12,000.

## Adverse Effects of HBOT

Adverse events can occur during compression, treatment, and decompression and are related to the increased pressure and/or the increased oxygen concentration.[67] Complications such as pulmonary barotrauma or seizures can occur seen immediately, but more subtle adverse effects may emerge after a series of treatments. The findings of a recent study of HBOT for acute carbon monoxide poisoning (which is not covered in this report) raise concerns over worse cognitive outcomes in patients receiving HBOT compared to normobaric oxygen.[68]

## Rationale for Use HBOT in Brain Injury

In chronic infected or nonhealing soft tissue wounds, local tissue hypoxia predisposes to infection and prevents effective healing.[56] Hyperbaric oxygen reverses local hypoxia, inhibits postischemic vasoconstriction, and promotes the formation of collagen matrix, which is essential for angiogenesis and restoration of blood flow to the injured tissue.[55-57] Although the biochemical and cellular effects of oxygen deprivation and oxygen therapy are well-accepted for soft tissue injuries, the application of these concepts to brain injuries is controversial. Recent theories of neuronal damage and recovery implicate a complex cascade of events that begin with depletion of intracellular ATP and expression of immediate early genes leading to energy failure, mitochondrial dysfunction, oxidative damage to RNA/DNA, and functional or structural brain damage.[69]

A detailed examination of the theoretical basis for the use of HBOT in brain injury is beyond the scope of this report. The theories of brain pathophysiology and recovery from injury, along with the animal experimental studies and human case studies supporting these theories, have been reviewed in detail elsewhere.[70] The following discussion is not comprehensive, but highlights some of the underpinnings of these theories and how they differ from other theories of brain injury and recovery.

**Acute Brain Injury.** Inadequate supply of blood and oxygen clearly causes injury and cell death in stroke, in which the artery supplying a region of the brain is blocked, and in anoxic-ischemic encephalopathy, in which perfusion to the entire brain is compromised by shock, hypotension, strangling, or another insult. In acute traumatic brain injury, hypoxia and hypotension are each independently associated with increased mortality and morbidity. Thus secondary ischemia and oxygen deficiency are thought to be important mechanisms of cell death in traumatic brain injury.[40]

Because of the devastating effects of hypoxia and hypotension in brain-injured patients, aggressive efforts to avoid or correct hypovolemic shock and to prevent cerebral hypoperfusion became fundamental principles of the management of trauma care. These principles, however, have recently been challenged by studies suggesting that management of perfusion pressure does not improve, and may worsen, the outcome of resuscitation. However, aggressive management of trauma reduces the frequency of hypoxic and ischemic episodes, but does not come close to eliminating it. For this reason, there is renewed interest in finding more effective strategies for ensuring adequate oxygenation and redistributing cerebral blood flow to injured areas of the brain.

Immediately after a brain injury, brain cells can be inactivated temporarily by local, injury-related sequelae such as ischemia and edema which are thought to compromise local perfusion.[5] This observation forms part of the rationale for the use of HBOT, which increases blood flow to the damaged areas of the brain, as documented by serial Single Photon Emission Computed Tomography (SPECT) scans and other techniques.[71-74]

In some experimental models of acute cerebral ischemia and acute carbon monoxide poisoning, HBOT prevents cell death.[70] The mechanism is unclear. Even if redistribution of cerebral blood flow is a factor, the effects of oxygen on the cellular and inflammatory response to injury may be more important.[70] Recently, for example, in a rat model of focal cerebral ischemia, HBOT reduced brain leukocyte myeloperoxidase (MPO) activity, which is produced by white blood cells (polymorphonuclear neutrophils) and is a marker of the degree of inflammation. Rats randomized to HBOT had reduced infarct size and improved neurological outcomes compared with untreated rats, and the degree of neurologic damage was highly correlated with the level of MPO activity.[75] In a separate model of cardiac arrest and resuscitation, the same investigators found that dogs treated with HBOT had better neurological outcomes and, histologically, fewer dying neurons than dogs treated conventionally.[76] The magnitude of neuronal injury correlated well with the neurological outcomes, but was not related to cerebral oxygen delivery or to the rate of oxygen metabolism.

**Chronic Brain Injury.** Many brain-injured patients progress spontaneously from coma to consciousness to recovery of some cognitive functions. This phenomenon of spontaneous recovery from brain injury implies that some brain cells that have lost function can regain it, sometimes after long periods of time. Several theories of recovery after injury in the central nervous system invoke the concept of temporary, reversible inactivity of brain tissue to explain this phenomenon.

The use of HBOT for chronic brain injury, cerebral palsy, and stroke is based on the theory that, in any brain injury, there are inactive cells that have the potential to recover. According to this theory, these "idling neurons" exist in the ischemic penumbra, a transition area of dormant neurons between areas of dead tissue and the unaffected healthy tissue.[70, 74, 77-79] The theory is that oxygen availability to these cells stimulates the cells to function normally, reactivating them metabolically or electrically.

It is useful to distinguish between this theory and a popular theory in the field of neuropsychology. Both theories invoke the concept of temporary inactivation of neurons, but the neuropsychological theory postulates that the neurons are inactivated by deprivation of innervation that had come from cells now destroyed by TBI.[5] According to this theory, recovery occurs as surviving neurons establish new synaptic connections that can help reactivate cells that are temporarily inactive. Terms such as synaptic reorganization and collateral sprouting are used to describe the process of increasing the number and complexity of these synaptic connections.

This concept arose from observations in animal studies demonstrating growth and reorganization of surviving hippocampal cells after surgical elimination of afferent excitatory input.[80] It was first applied by Russian physicians and psychologists treating soldiers injured in World War II.[81] These early efforts form the basis for "restorative" cognitive rehabilitation and other therapies that aim to restore (rather than compensate for) brain functions that have been lost due to injury.

Recently, a National Institutes of Health Consensus Development Conference conducted an independent, critical assessment of the animal and human evidence regarding this theory and clinical approaches based on it.[5] The panel noted, first, that synaptic reorganization and

"sprouting" observed in the denervated animal brain had not been translated into functional improvements. Second, they noted the lack of evidence that any therapy actually promotes these physiologic processes, either in animal models or in humans. No animal experiments or human case studies have succeeded in linking the clinical observation of improved cognitive function with anatomic or physiologic measures of synaptic enrichment. In fact, human studies have found no relationship between the amount of treatment, frequency of family visits, or other forms of stimulation hypothesized to promote the growth of new synaptic connections. Regarding clinical evidence, the panel found "a notable lack of scientific data concerning the effectiveness of [restorative] interventions. On balance, the limited data available have also been equivocal with respect to the effectiveness of restorative approaches."[5] Subsequently, in a randomized trial in 120 active duty military personnel with moderate to severe TBI, intensive in-hospital cognitive rehabilitation was no more effective than limited home rehabilitation program with weekly telephone support from a psychiatric nurse.[82]

In contrast with the cognitive stimulation theory, the "idling neuron" theory views neuron inactivity denervation as the result of chronic hypoxia, and postulates that restoring oxygen stimulates the growth of blood vessels and of new synaptic connections among previously dormant neurons. Supporters of the use of HBOT in brain injury, argue that this theory has a stronger experimental base than the theory underlying restorative cognitive therapies.[70] In contrast to the theoretical effects of cognitive stimulation, the effects of the proposed treatment—pressurized oxygen—can be observed directly in animal models. As noted above, animal studies have examined HBOT's effects on physiologic and anatomic endpoints, including neuronal death, infarct size, and, in some models, development or preservation of synapses. The physiologic effects of hyperbaric oxygen have also been examined in before-after treatment case studies in humans using SPECT imaging and markers of cerebral metabolism.[72, 74, 83]

# Chapter 2. Methodology

## Technical Expert Advisory Group

We identified technical experts to assist us in formulating the research questions and identifying relevant databases for the literature search. The expert panelists, who are listed in Appendix B, included a neurologist specializing in stroke, a neurosurgeon specializing in severe brain injury, a pediatric neurologist with expertise in treating patients with cerebral palsy, and a physician with an HBOT practice. Throughout the project period, we consulted individual members of the technical expert advisory group (TEAG) on issues that arose in the course of identifying and reviewing the literature.

## Scope and Key Questions

The specific questions addressed in this report are:

1. Does HBOT improve mortality and morbidity in patients who have traumatic brain injury or nontraumatic brain injury, such as anoxic ischemic encephalopathy?

2. Does HBOT improve functional outcomes in patients who have cerebral palsy? (Examples of improved functional outcomes are decreased spasticity, improved speech, increased alertness, increased cognitive abilities, and improved visual functioning.)

3. Does HBOT improve mortality and morbidity in patients who have suffered a stroke?

4. What are the adverse effects of using HBOT in these conditions?

To identify the patient groups, interventions, and outcomes that should be included in the review, we read background material from diverse sources including textbooks, government reports, proceedings of scientific meetings, and Web sites. We also conducted focus groups and interviews to improve our understanding of the clinical logic underlying the rationale for the use of HBOT. In the focus groups, we identified outcomes of treatment with HBOT that are important to patients, caregivers, and clinicians and examined whether patients, caregivers, and clinicians who have experience with HBOT value certain outcomes differently from those who have not used HBOT. The methods and results of the focus groups are reported in Appendix C.

The following interventions, populations, outcomes, and study designs were used to formulate the literature search strategy and to assess eligibility of studies.

## Intervention

- Hyperbaric Oxygen Therapy: any treatment using 100 percent oxygen supplied to a patient inside a hyperbaric chamber that is pressurized to greater than 1 atm; any frequency, duration, and total number of treatments.

## Population

- Patients with brain injury from any cause and in any stage (acute, subacute, or chronic).
- Patients with cerebral palsy of any etiology.
- Patients with thrombotic stroke, excluding patients with transient ischemic attack (TIA), hemorrhage (e.g., subarachnoid hemorrhage), or vasospasm.
- Patients with progressive neurologic diseases (i.e., multiple sclerosis, Parkinson's disease, Alzheimer's disease, and chronic cerebral insufficiency), acute infectious processes (i.e., mucormycosis), radiation sensitization of brain tumors, and reports of treating eye damage or sudden deafness were excluded.
- The use of HBOT for approved indications such as acute carbon monoxide poisoning or acute air embolism was also excluded.

## Outcomes

We sought articles reporting any clinical endpoint. In general we excluded studies that reported only intermediate outcomes, such as changes in cerebral metabolism or EEG findings. However, we included studies that reported the effect of HBOT on elevated intracranial pressure, an intermediate outcome that is currently a main determinant of treatment in current clinical practice.

## Design

- We included studies of human subjects that reported original data (no reviews of studies).
- We used the algorithm in Figure 1 to classify the design of studies. All of the study designs in the figure were included in the review except for non-comparative studies (e.g., case reports).
- Before-after or time-series studies with no control group were included if (a) five or more cases were reported, and (b) outcome measures were reported for both the pre- and post-HBOT period.

# Literature Search Strategy

## Electronic Database Literature Search

We searched a broad range of databases to identify published and unpublished studies of the effectiveness and harms of HBOT in patients with brain injury, cerebral palsy, and stroke. Each database initially was searched from its starting date to March 2001. Full details of all the strategies, the databases searched, the inclusive dates searched, the software used to search, and the number of citations found that were used in this review are provided in Appendix D.

The databases we searched were:

- MEDLINE
- PreMEDLINE
- EMBASE

- HealthSTAR (Health Service Technology, Administration and Research)
- CINAHL (Cumulative Index to Nursing & Allied Health)
- Cochrane Database of Systematic Reviews
- Cochrane Controlled Trials Register
- DARE (Database of Abstracts of Reviews of Effectiveness)
- AltHealthWatch
- MANTIS (Manual, Alternative and Natural Therapy)
- Health Technology Assessment Database

If only studies found in the large electronic databases are included, a publication bias may arise in the review. Studies with a positive and statistically significant finding are more likely to be published than those finding no difference between the study groups.[84] Because small studies are more likely to have negative results, this bias has also been called "sample size bias."

Excluding "gray literature" is another potential source of bias. The term "gray literature" refers to reports of studies that are difficult to find, largely because they either are unpublished or are published in sources that are not indexed by the large electronic databases. The Interagency Gray Literature Working Group described gray literature as "foreign or domestic open source material that usually is available through specialized channels and may not enter normal channels or systems of publication, distribution, bibliographic control, or acquisition by booksellers or subscription agents."[85] Studies found in the gray literature are not inherently lower quality than those identified through electronic methods, although they are more likely to be small and to have inadequate power to show a difference if one exists.

To avoid publication bias, we asked TEAG members to identify additional databases as potential sources of other material, particularly gray literature, meeting abstracts, and conference proceedings, that may not be indexed in other electronic databases such as MEDLINE. They identified the following sources:

- The Undersea & Hyperbaric Medical Society: a large bibliographic database (30,000 records), http://www.uhms.org/library.htm
- The Database of Randomised Controlled Trials In Hyperbaric Medicine, http://hboevidence.com/
- European Underwater and Baromedical Society, http://www.eubs.org/
- International Congress on Hyperbaric Medicine, http://www.ichm.net/
- National Baromedical Services, Inc.

Each organization was contacted regarding searching their databases. A search of the Undersea & Hyperbaric Medical Society database was conducted by its librarian using our search strategy. A search of the Database of Randomised Controlled Trials in Hyperbaric Medicine was conducted online by the principal investigator. A TEAG member provided the proceedings for 11 of the 12 International Congress on Hyperbaric Medicine conferences (Proceeding number 1 is no longer available). National Baromedical Services, Inc., conducted a search of its database and sent a list of titles at the request of one of the TEAG members. The European Underwater and Baromedical Society did not respond to our requests for access to its database.

## Hand Searches

The references of all papers were hand searched. In addition, two reviewers independently conducted hand searches of the references from the *Textbook of Hyperbaric Medicine*.[60] One TEAG member provided articles and meeting abstracts from his personal library. These submitted articles and abstracts were also independently assessed for inclusion by two reviewers.

## Update Searches

Update literature searching of the electronic databases MEDLINE, PreMEDLINE, EMBASE, CINAHL, the Cochrane Library, and the Health Technology Assessment Database was completed on February 26, 2002, using the same search strategy as used for the initial searches. The results of these searches are summarized in Appendix D. In May 2003, we added eight additional publications brought to our attention by a peer reviewer. Finally, a supplemental search of MEDLINE, PreMEDLINE, EMBASE, and CINAHL was conducted in July 2003.

# Management of References

As such a wide range of databases was searched, some duplication of references resulted. To manage duplicate citations, the titles and abstracts of the bibliographic records were downloaded and imported into Reference Manager, Version 9 (ISI ReSearch Soft, USA), a reference management software program. Due in part to the relatively high proportion of meeting abstracts, some studies present data duplicated in another publication. Where this is clearly the case, only one set of data is presented in the Evidence Tables, and the duplicate publications are noted. Abstracts reporting the same data as found in a full paper were not included. Where multiple publications presented different data from a single study, all were included.

# Assessment of Papers for Eligibility

Two reviewers (MM and SC) independently assessed each title and abstract located through the literature searches for relevance to the review, based on the intervention, population, outcome, and study design criteria listed above. Due to time and budget constraints, only studies originally published in the English language were considered for review. This decision was made by the funding agency, AHRQ.

We retrieved the full-text article, report, or meeting abstract of all citations that met the eligibility criteria. Independently, two reviewers reapplied the eligibility criteria to these materials. Disagreements were resolved through consensus.

# Data Extraction

Extraction of data from studies was performed by one reviewer (MM for head injury and cerebral palsy, and SC for stroke) and checked by a second reviewer (SC and MH for head injury and cerebral palsy, and MM for stroke). Disagreements were resolved through consensus. Data extracted include first author, year, study population, HBOT protocol, other interventions, study

design, number of patients, outcomes measured, baseline and followup details, results, adverse effects reported, and general comments of the reviewers.

## Assessment of Study Validity

All trials were assessed using a list of items indicating components of internal validity in a standardized fashion, based on validity checklists developed at the National Health Service Centre for Reviews and Dissemination and by the US Preventive Services Task Force (Appendix D).[86, 87] Internal validity indicates the level of confidence we have in the accuracy (validity) and reliability (or reproducibility) of the results of the study. The internal validity of a study is assessed based on criteria set for a specific study design. In this way, an observational study would not be judged by criteria for randomized controlled trials (RCTs), but rather by criteria that apply to—and can be met by—a good-quality observational study.

For RCTs and nonrandomized controlled trials, the items assessed for internal validity were randomization/allocation concealment (e.g., randomization and concealment procedures, stratification), baseline comparability of groups, timing of baseline measures, intervention, outcome measures, timing of followup measurements (long enough to assess effects), loss to followup, handling of dropouts or missing data, masking, statistical analysis (if any), and general reviewer comments. The rationale for selecting these criteria is as follows:

- **Methods used to ensure comparable groups at baseline.** Some methods of allocating subjects to treatment and control groups are more likely to prevent bias and to result in groups that are comparable at baseline. Randomization, the best method to allocate patients to groups, is most effective if it is *concealed*. (The importance of allocation concealment is discussed in detail in the Results section in reference to controlled trials of HBOT for traumatic brain injury.)

- **Baseline comparability of groups.** The purpose of randomization (or another allocation method) is to distribute prognostic characteristics equally in the treatment and control groups. Effective randomization distributes known as well as unknown prognostic factors in an unbiased manner. We judged studies on how thoroughly they reported baseline characteristics known to affect prognosis and on whether there were baseline differences between the groups. In a small, well-conducted trial, groups may differ in important baseline prognostic factors because too few patients were randomized. In a large trial, even small differences in baseline characteristics raise concern that randomization failed to distribute unknown prognostic factors equally among the groups. When the method used to conceal allocation is inadequate or is not described, such differences may suggest that randomization was subverted or carried out incorrectly.

- **Use of validated outcome measures.** The use of validated, reliable outcome measures prevents bias on the part of persons who assess outcomes. The use of measures that have not been shown to be valid and reliable reduces confidence that the findings are accurate.

- **Masking of outcome assessment.** The investigators who judge whether the patients have improved should not be aware of which patients received the treatment. This

masking or blinding of outcome assessment is important, because strong beliefs about the benefits of the treatment can influence an observer's assessment of a patient's condition.

- **Maintenance of comparable groups.** Exclusion of subjects after randomization, high rates of loss to followup, and failure to include all randomized patients in the analysis of study results can compromise the quality of a study. Including only those patients who completed the study can give an incomplete picture of the effects of the treatment. For example, if 100 patients are treated and 10 respond, 30 do not respond, and 60 quit the study before their response can be measured – and of these, 20 suffer an adverse event and have to quit treatment – the overall response rate to therapy might be as low as 10 percent. If only those patients who finished the study were included in the statistical analysis, it would appear that the response rate is 25 percent (10/40), when in fact it might have been much lower.

For observational studies, items assessed for internal validity were the establishment of a stable baseline (for before-after and time series studies) or the baseline similarity of the compared groups (if a comparison group was included); discussion of or control for potential confounders; exposure measurement (were all subjects given the same HBOT treatment?); other interventions, the use of valid outcome measures; and the timing of followup measurements.

- **Establishment of a stable baseline.** A before-after treatment study or a time series study relies on the premise that the results after treatment are better than could be expected with standard medical care and the passing of time. For a reader to accept this premise, the study must describe thoroughly the baseline condition of the patients, other aspects of care management, the degree of social support, and any other factor that might predict the outcome. The baseline condition of the patients must be established to be stable; otherwise, changes seen cannot be distinguished from an evolving clinical picture. Omission of even one characteristic that could have accounted for the results raises doubt about whether it was really the treatment that is responsible. The baseline assessments should be timed in a manner that is appropriate to the study's circumstances. For example, the baseline assessments would need to be more frequent in a study of patients being treated in an intensive care unit for acute trauma than in a study of patients who have motor, language, and cognitive deficits many years after trauma.

- **Discussion of or control for potential confounding factors.** In conducting an observational study, the investigators should plan to measure factors other than the use of HBOT that could explain the observed results. Such factors include baseline prognostic characteristics, the natural course of the disease, and the use of other interventions.

  Because they do not use randomization to distribute prognostic factors equally among treated and untreated groups of patients, observational studies usually compare groups that have important baseline differences. For this reason, it is important that baseline characteristics be assessed and reported in detail. When baseline differences are apparent, failure to use appropriate methods to control for bias reduces the internal validity of a study.

  In addition to prognostic factors, differences in the intensity and quality of care can also influence the results of observational studies. In observational studies, treatment

regimens are not determined experimentally but rather by the clinician and patient involved, and they may vary widely between and within groups. Because practice styles vary in many ways, not just in the use of HBOT, other interventions may be used differently and they may have their own impact on outcomes. The interventions used in both groups must be described thoroughly. If differences in management styles and the quality of care are not described, or if they are great, it may be impossible to determine the extent to which the observed results are due to HBOT or to other aspects of care.

- **Use of valid outcome measures and masking of outcome assessment.** The use of validated, reliable outcome measures, rather than the investigator's global subjective judgment, is even more important in observational studies than it is in a RCT. In before-after studies and in many other types of observational studies, the patients, their caregivers, and the investigators are *always* aware of treatment status. Although difficult, it is possible to obtain an independent assessment of results by having unbiased observers who did not participate in administering HBOT rate videotaped examinations made before and after treatment.

Based on these criteria, each study was assigned an overall rating (good, fair or poor) according to the US Preventive Services Task Force methods.[87] The definitions of the three rating categories for these types of studies are as follows.

**Good**: Comparable groups assembled initially (adequate randomization and concealment, and potential confounders distributed equally among groups) and maintained throughout the study; followup at least 80 percent; reliable and valid measurement instruments applied equally to the groups; outcome assessment masked; interventions defined clearly; all important outcomes considered; appropriate attention to confounders in analysis; for RCTs, intention-to-treat analysis.

**Fair**: Generally comparable groups assembled initially (inadequate or unstated randomization and concealment methods) but some question remains whether some (although not major) differences occurred with followup; measurement instruments acceptable (although not the best) and generally applied equally; outcome assessment masked; some, but not all important outcomes considered; appropriate attention to some, but not all potential confounders; for RCTs, intention-to-treat analysis.

**Poor**: Groups assembled initially not close to being comparable or not maintained throughout the study; measurement instruments unreliable or invalid or not applied equally among groups; outcome assessment not masked; key confounders given little or no attention; for RCTs, no intention-to-treat analysis.

The discussion of results and conclusions in this report is based on good- and fair-quality studies. Flaws that have bearing on the interpretation of studies included in this review are discussed in the text and can be examined in Evidence Tables 8 and 9. Results of good-quality studies have a high likelihood of being both valid and reliable. Fair-quality studies have important but not fatal flaws in their design or conduct. The category of fair is broad, with some studies that are probably valid and others that are unlikely to be valid, depending on the specific

flaws found and their severity. The inadequacies found in poor-quality studies make the results unreliable.

External validity refers to the applicability of the results of the study to clinical practice. Although criteria for assessing external validity in systematic reviews are not well-defined, a few criteria can be identified. First, the investigators should describe the criteria used to identify eligible subjects for the study. Second, they should report the numbers of patients who were considered for inclusion in the study, the number that met the eligibility criteria, and the number that actually entered the study. Third, they should report the age range, the severity of disease or disability, the prevalence of comorbid conditions, and other sample characteristics that would enable a clinician to assess the applicability of the results to the patient population for which the intervention is intended.

## Quality of the Body of Evidence

We assessed whether the overall strength, quality, and consistency of the body of evidence for each key question. This assessment was based on the internal validity and external validity of the individual studies and the coherence of all the pertinent studies taken as a whole. We also assessed whether the body of evidence was sufficient to provide a clear answer to the key question. In this context, the term "insufficient evidence" refers to the fact that important gaps in the available information remain; this term should be taken to mean that the evidence neither proves nor disproves that HBOT is effective.

## Synthesis of Results

Results of data extraction and assessment of study validity are presented in structured tables (Evidence Tables 1-9) and also as a narrative description. We considered the quality of the studies and heterogeneity across studies in study design, patient population, interventions, and outcomes to determine whether meta-analysis could be meaningfully performed. If meta-analysis could not be performed, we summarized the data qualitatively. Assessments of individual criteria for each included study are presented in Evidence Tables 8 and 9, along with the summary measure assigned.

## Peer Review

The draft document was sent out for peer review to national experts (see Appendix B.) Their comments were reviewed and, where possible, incorporated into the final document. The final document has not undergone a second review by these reviewers.

# Chapter 3. Results

## Studies Meeting Eligibility Criteria

The literature searches, both electronic and by hand, identified over 900 references relating to HBOT and brain injury, cerebral palsy, or stroke. These references/abstracts were assessed against the inclusion criteria, and 197 full papers were obtained. Upon examination of the full papers, 75 were excluded (see Appendix E) because they did not meet the inclusion criteria. Sixteen studies were excluded because they did not report any health outcomes; most of these reported intermediate outcomes such as cerebral metabolism changes. These studies are listed in Appendix F. We were unable to retrieve 16 titles (see Appendix G). These were incomplete or inaccurate citations identified through hand searching. In total, 71 studies met inclusion criteria, reported in 73 publications (Figure 1). Descriptions of the outcome measures reported in the included studies are given in Appendix H.

The studies are described in Evidence Tables 1 through 7. Evidence Tables 1 through 6 refer to studies for which we found full articles. We found three controlled trials and nine observational studies of patients who had brain injury, two controlled trials and three observational studies of cerebral palsy, and five controlled trials and 17 observational studies of stroke. Evidence Table 7 summarizes studies that have been published only as abstracts (12 on stroke, 15 on brain injury, and five on cerebral palsy).

The quality assessment of included studies is presented in Evidence Tables 8 and 9. Evidence Table 8 includes controlled trials, while Evidence Table 9 includes observational studies. The quality of studies available only in abstracts could not be assessed.

## 1. Does HBOT improve mortality and morbidity in patients who have traumatic brain injury or nontraumatic brain injury, such as anoxic ischemic encephalopathy?

### Traumatic Brain Injury

#### Controlled Trials

**Mortality and morbidity results.** The best evidence of the effect of HBOT on mortality and morbidity in TBI comes from two fair-quality randomized controlled trials (see Evidence Table 1). The first trial found that HBOT had no effect on mortality at 12 months.[88] In the more recent trial, there was a dramatic decrease in mortality 12 months after treatment, but HBOT did not improve the rate of a favorable functional outcome.[89-91]

**Artru, Chacornac, and Deleuze (1976)[88]** studied 60 patients with coma due to head injuries. These patients were stratified into nine subgroups based on the severity of coma and the presence of mass lesions and then were randomized to HBOT or to standard therapy. The stratification resulted in groups that were similar in terms of type of injuries, but the authors did not report whether the two resulting groups were similar in other important prognostic variables. After 12 months of followup, overall mortality was similar in both groups. The rate of recovery of consciousness at 2 weeks and 1 month was higher in the HBOT groups (42 percent vs. 28 percent), but this finding was not statistically significant.[88] The mean duration of coma was

also shorter in the HBOT group but was not statistically significantly different (28.2 days vs. 32.7 days, p = NS). In one of nine subgroups, patients under 30 years old with brain stem contusion were more likely to recover consciousness by 1 month if they received HBOT. There were nine patients in each group; one died in each group, and there were six conscious in the HBOT group and one conscious in the control group at 1 month ($p < 0.03$).

**Table 2. Results for Study by Artru, Chacornac, and Deleuze**

| | HBOT Group | Control Group |
|---|---|---|
| **Died within 1 year** | **15/31** | **16/29** |
| **Conscious at 1 month** | **13/31** | **8/31** |
| **Independent in daily activities at 1 year among survivors** | **14/31** | **12/29** |

**Rockswold, Ford, et al. (1994)**[89-91] enrolled 168 of 272 (62 percent) potentially eligible patients with acute closed-head trauma. Of the 272 potentially eligible patients, 18 percent died within 6 hours of admission, 8 percent had contraindications to HBOT, 6 percent were not identified as potential subjects in time for randomization within 6 hours of admission, and consent could not be obtained for 6 percent (no details given on the baseline characteristics or outcome of these patients).

The 168 patients who were randomized had Glasgow Coma Scale Scores of 9 or less, 6 to 24 hours after admission with a severe head injury, or 6 to 24 hours after deterioration following admission for what appeared to be a mild or moderate injury.[89-91] This study did not describe the methods used to randomize patients. There were several differences between the HBOT and control groups at the start of the study. For example, more patients in the control group had an operative mass lesion (39 percent vs. 49 percent), while more patients in the HBOT group had intracranial pressures above 20 mm Hg (52 percent vs. 46 percent). Overall, the differences in prognostic variables did not seem to favor either the HBOT group or the control group. The authors did not report whether patients enrolled after deterioration were distributed evenly (these patients may have a worse prognosis, the results of the trial could be biased if they were not distributed equally in the two groups).

The main results of the trial are summarized in Table 3. After 1 year, patients who were assigned to HBOT treatment had lower mortality (17 percent vs. 31 percent), but there was no difference in the proportion of patients who were either dead or severely disabled. Additional analysis showed that HBOT reduced mortality in patients who had a GCS score of 4 to 6 or ICP > 20 mm Hg, but not in other subgroups of patients.

**Table 3. Results of Study by Rockswold, Ford, et al.**

| | HBOT Group | Control Group |
|---|---|---|
| **Died within 1 year** | **14/84** | **26/84** |
| **Dead or severely disabled at 1 year** | **40/84** | **40/84** |

Differences between these two studies might explain the discrepant mortality results. First, Artru was a much smaller study and could have missed an important difference in mortality. Second, the HBOT protocols differed among these studies. The Rockswold trial used 1.5 atm, while the Artru study used 2.5 atm.[88] In the Rockswold trial, patients were treated for 60 minutes every 8 hours for 2 weeks or until the patient regained consciousness or died. In the

Artru trial, treatments were given daily for 10 days,[88] followed by 4 days without treatment, followed by 10 days of treatment until the patient regained consciousness or died. Third, in most cases Rockswold began treatment within 24 hours of injury, while in Artru there was an average delay of 4.5 days between the onset of coma and the start of HBOT.

It is important to note that the control patients in Artru et al. had higher mortality (about 50 percent) than the control patients in Rockswold (34 percent). This could be due to differences in baseline prognosis or to differences in the standard treatments given to control patients. Unfortunately, it is difficult to compare the prognoses of the patients in the two studies, because the two studies used different scales to assess the prognosis of the head injury and provided different information about associated injuries and other comorbidity. Rockswold used the Glasgow Coma Scale, while Artru used a modified Jouvet scale. The two scales are said to be poorly correlated.[92]

It is also difficult to compare the standard treatments given to patients in the control group. Because of the spread in the years of publication (1976 to 1994) and the different countries involved, it can be assumed that these treatments may have varied considerably. For example, in the more recent Rockswold trial, all patients had invasive ICP monitoring and phenytoin. In the Artru study, most patients in both groups received furosemide and mannitol, but these decisions were based on clinical judgments about the likelihood of elevated ICP.

Differences in study quality are unlikely to explain the discrepant results of the trials, but the limitations of both trials make the validity of their results uncertain. Of the two trials, Rockswold had better internal validity (that is, quality), because it masked outcome assessors and reported how the patients were selected from the potential pool of eligible patients and how many refused enrollment.[90] Neither study described the methods used to randomize patients. Some methods of randomization cannot prevent investigators from (knowingly or unknowingly) placing patients with a more favorable prognosis into the treatment group. Empirical evidence has shown that studies that do not describe the method of randomization report exaggerated effects.[93] This flaw is particularly important in studies of comatose trauma patients, because an experienced clinician can predict prognosis within groups of patients who have a similar severity-of-illness score.

**Effect of HBOT on physiologic measures.** In the Rockswold trial, nearly all of the observed reduction in mortality occurred in the subgroup of patients who had ICP $\geq$ 20 mm Hg prior to treatment.[89-91] One important question is whether this benefit corresponded to a reduction in ICP in these subjects. The measurements were taken every 15 minutes during HBOT and then hourly until the next treatment, and hourly in the control group. The mean peak ICP values in controls (no HBOT) and HBOT-treated patients were not significantly different. However, mean peak ICP was significantly lower for patients who received HBOT and myringotomy (n = 42) versus patients who received only HBOT (n = 37) and versus controls (22.2 mm Hg in HBOT plus myringotomy vs. 33.0 in HBOT alone and 30.3 in controls, $p < 0.05$). The authors theorized that the pain caused by increased otic pressure contributed to the maintenance of elevated ICP, and that the effect of HBOT can be seen once prophylactic myringotomies are performed. The time to the mean peak ICP in the two groups was not reported. The duration of effect was not clear. Comparisons to other specific treatments for elevated ICP given to control patients were not reported. The number of subjects with HBOT plus myringotomy, reported in Table 3 in the paper, differs from the number reported in the text.

Other physiologic parameters of the effect of HBOT in traumatic brain injury include cerebral blood flow, the arteriovenous oxygen difference, the cerebral metabolic rate of oxygen,

and the distribution of cerebral blood flow as visualized by a SPECT scan. The correlation of clinical outcomes with these measures has not been examined in controlled trials of HBOT for traumatic brain injury.

## Observational Studies

We found six observational studies of HBOT in human patients with TBI (see Evidence Tables 2 and 9). Five of these studies compared the conditions of a single group of patients before and after HBOT treatment.[94-98] The other compared two groups of patients, one of which was treated with HBOT.[99]

In most of these studies, the main research goal was to examine the short-term effect of HBOT on physiologic parameters, sometimes with the goal of examining whether a correlation between physiologic parameters and patients' outcomes was observed. These studies reported outcomes incompletely and often provided no information on how assessments of outcome were made. None of the studies masked the assessment of clinical outcomes or of prognostic measures, such as GCS, that are known to have low inter-rater reliability and are therefore subject to bias. (Both of these methodological precautions can be accomplished in prospective studies whether or not they are randomized controlled trials.)

**Artru, Phillipon, et al. (1976)**[94] recorded cerebral blood flow and three measures of cerebral metabolism before and after one to three hyperbaric oxygen treatments at 2.5 atm in six patients suffering from coma due to TBI. The duration of the followup period was not stated, but the authors state that three of the subjects died, one lived but did not recover consciousness, and two lived and recovered consciousness but had serious psychiatric or neurologic sequelae. There was no relationship between these outcomes and pre-HBOT cerebral blood flow and metabolism or post-HBOT cerebral blood flow and metabolism. In general, changes in blood flow or metabolism after HBOT were small, inconsistent in direction, and of no clear clinical consequence. The two subjects who recovered consciousness eventually were also the only subjects who had temporary neurological improvement immediately after a hyperbaric treatment. One of these two patients had increases in cerebral oxygen consumption and blood flow after HBOT, and the other had decreases in these measures. The findings suggest that the results of a single treatment, or a short series of treatments, do not correlate with the clinical outcome.

**Hayakawa, Kanai, et al. (1971)**[95] studied 13 comatose brain-injured patients, nine of whom suffered from TBI. (Because these nine were not reported separately, we used data from all 13 subjects.) Cerebrospinal fluid pressure (CSFP) was measured before, during, and after treatment with 2 atm for 1 hour. Baseline CSFP ranged from 20 to 40 mm Hg. In two of the subjects, CSFP was 5 mm Hg higher than the pre-HBOT level; in two others, it was 5 mm Hg lower after treatment; and in the remainder, it was similar to the pre-HBOT level. The investigators provided no information about the clinical responses of these patients, but state "When [HBOT] produced a major change in CSFP, the neurological deficit of the patient was mild and the clinical improvement with OHP (oxygen under hyperbaric pressure) was remarkable. On the other hand, when CSFP was little changed by OHP, there was little clinical improvement and the patient commonly had extensive brain damage."[95]

It is unclear whether this statement refers to patients who had a decrease in CSFP during treatment that rebounded to baseline or higher values by the end of treatment, or to some other pattern of response. Even if the correlation between the CSFP response and clinical outcome were valid, it would not be clear that the CSFP response to HBOT was a cause of a good

prognosis. Because the investigators did not report clinical outcomes or a measure of the baseline severity of injury, we rated the study as poor-quality. These deficiencies make it impossible to determine how the investigators decided that a subject improved clinically or whether those with milder injury were more likely to improve. Finally, since this study was performed, intracranial pressure monitoring has supplanted measurement of CSFP, and CSFP has been found to be a poor indicator of intracranial pressure.

**Mogami, Hayakawa, et al. (1969),**[96] by the same group as Hayakawa et al., is a poor-quality, retrospective before-after study of 66 brain-injured patients, 51 of whom had head injury. The study provides no useful scientific information about the effect of HBOT treatment. The study results are uninterpretable, because prognostic information about the subjects before treatment is inadequate. The pretreatment injury severity was not described, but it is likely that the sample consisted of subjects with mild, moderate, and severe injuries. The main outcome measures were whether the patient improved. Improvement was classified as "great," "some," or "none." The timing of assessment and the criteria used to classify subjects' condition were not described, other than to say that the assessment included mental as well as neurological function. It appears that many of the improvements were in "awareness and responsiveness." Only patients who had mild deficits improved, while in those who were "in deep coma" the improvements "were hardly noticeable."

In a retrospective cohort study, **Ren et al (2001)**[99] examined the effect of HBOT on 35 subjects with severe TBI (GCS < 8) who had HBOT, with 20 control subjects. The primary outcome measure was functional status, measured by the Glasgow Outcome Score 6 months after treatment; mean change in GCS was reported as a secondary outcome measure. We rated the study poor-quality because it lacked a well-defined inception cohort and excluded subjects who died after the analysis. Because the study was not randomized, it would be important for the investigators to make clear why some patients were treated with HBOT and others were not. For example, if patients were selected on the basis of the availability of the HBOT unit on a particular day, selection bias would not be expected to be a major problem. On the other hand, if patients were selected for HBOT because they were better candidates, prognostic factors in the control and treatment groups would be unequal and would probably favor the HBOT group. The investigators did not explain why there were uneven numbers of patients in the groups (35 vs. 20) and provided no details on how patients were selected for inclusion in control or intervention groups. In the comparison data presented in the article, the GCS was similar in the two groups, but there were more women in the HBOT group (29 percent vs. 15 percent) and some differences in computerized tomography (CT) findings (see Evidence Table 2). Whether or not they are significant prognostic factors in themselves, these differences suggest that the compared groups do not represent a single population of patients, as do the subjects of a controlled trial with clear, specific inclusion criteria and random allocation to treatment groups.

The Ren study found significant improvement in the mean GCS after one and three treatments ($p < 0.01$ for both) in the HBOT-treated group, where the mean GCS was 5.1 at baseline and 14.6 after three treatments. No significant difference in mean score was found in the control group, with a mean GCS of 5.3 at baseline and 9.5 after three courses of treatment. At 6 months, a significantly higher proportion of HBOT-treated subjects had mild disability as measured by the Glasgow Outcome Score ($p < 0.001$).

**Rockswold et al. (2001)**[97] measured cerebral metabolism, cerebral blood flow, and intracranial pressure before and up to 6 hours after HBOT treatment in 37 TBI patients who had a GCS $\leq$ 8. The investigators did not report morbidity and mortality outcomes. Instead, their

main goal was to record the effects of HBOT on physiologic measures and to determine how long these effects lasted. The protocol specified that each subject would be treated for 60 minutes at 1.5 atm when first eligible, then daily for up to 6 days. All patients in this study received prophylactic myringotomies prior to treatment.

The effect of HBOT on cerebral blood flow and metabolic measures was complex. In five patients who had low pretreatment cerebral blood flow, CBF levels were raised an average of 10 ml/100g/min for 6 hours after HBOT. In the 13 patients who had high pretreatment CBF, there were reductions (average about 10 ml/100g/min) that persisted for 6 hours. HBOT did not affect the arteriovenous oxygen difference (AVDO) in either of these groups of subjects. AVDO was higher for the first HBOT session than for subsequent sessions. For the 49 sessions in which CSF (cerebro-spinal fluid) lactate could be measured, there was an average decrease of 0.5 mmol/L 1 and 6 hours after treatment.

In patients with pretreatment ICP greater than 15 mm Hg, ICP rose during the HBOT session by an average of 7 mm Hg, then fell 1 hour after treatment by an average of 2 mm Hg compared with baseline. By 6 hours after treatment, the average reduction in ICP was 4 mm Hg. In patients with pretreatment ICP less than 15 mm Hg, there was a small (2 to 4 mm Hg) increase during and up to 6 hours after HBOT. The study does not provide data on the effect of HBOT on ICP beyond 6 hours post treatment.

This study provides fair-quality data about the duration of the physiologic effects of HBOT. The limitations of the study should also be noted. The study reported average responses for subgroups of subjects who had low or high baseline values of CBF and ICP. It would have been useful to report how many subjects in each group responded in the direction of the averaged group responses, how consistently individual patients responded, and how many subjects had a large response. For example, there were only 14 HBOT sessions in which the pretreatment ICP was higher than 15 mm Hg, and it is unclear from the article how many patients this represents and whether the average response represents a uniform drop over 14 sessions of some large responses combined with some non-responses or increases.

The lack of a separate control group is also a limitation of the study. A control group might have provided additional certainty that the changes in CBF and ICP after HBOT were due to HBOT. These parameters vary spontaneously among patients who have suffered serious brain injury. The main concern is that some of the observed changes after HBOT could be confounded by regression toward the mean—the tendency for abnormally high values to drop and abnormally low values to rise over time. At the very least, an independent control group would have been a useful comparison to assess whether the magnitude of changes in CBF, ICP, and other parameters measured after HBOT were greater than those that occur spontaneously in critically ill brain-injured patients.

The study provides no evidence on the question of whether the physiologic changes associated with HBOT are beneficial (or harmful) to patients. As noted by the authors, at some point during their stay, 44 percent of the subjects had an episode of intracranial hypertension (ICP > 20 mm Hg) for 20 minutes or longer. It is unknown, of course, whether this percentage would have been higher or lower in a group of similar subjects who did not receive HBOT.

**Sukoff & Ragatz (1982)**[98] is a poor-quality retrospective study of 50 patients, 10 of whom underwent continuous ICP monitoring. In the ICP-monitored patients, HBO treatments at 2 atm were given every 8 hours for 48 hours or every 4 hours if the ICP remained above 15 mm Hg. In the other patients, HBO was given every 8 hours for 2 to 4 days, depending on the clinical response.

The study was rated poor-quality because potential confounding factors were not addressed, outcome assessors were not masked, and data were presented selectively rather than according to a protocol. Detailed case descriptions are provided for the 10 patients who had ICP monitoring. ICP levels decreased for 8 patients during their hospital course, while two had ICP values near or higher than pretreatment at 2 hours post-treatment. The cases ranged widely in the severity of their injuries. The study provides no evidence that the improvements in ICP would be unexpected in the absence of HBOT. Some followup information is provided for some of the 10 patients, but again there is no indication that the reported outcomes are not consistent with the course of disease rather than attributable to hyperbaric treatments or any other therapy.

For the other 40 subjects, the authors reported that 22 "improved while undergoing their treatments" but provided no information about the criteria used to assess the response. Some had pre- and post-treatment CT scans; nine of these are described as showing "minimal improvement," but it is unclear whether this improvement was transient or whether the other six subjects had no improvement or had worsening of their CT scan findings. No followup data were provided on these 40 subjects.

### Abstracts and Conference Proceedings

Three trials[71, 100, 101] and four observational studies that included only TBI patients were reported only as meeting abstracts or conference proceedings (Evidence Table 7).[102-105] One trial reported improvements in at least some neurologic or functional outcomes, based on an undefined scale.[71] The other trial[100] classified each patient's outcome as a "cure," a "marked effect," a "positive effect," "no effect," or death. Cure was defined as "conscious, symptoms disappeared, and can care for self." Twenty-two of 32 (69 percent) in the HBOT group were cured, compared to 9 of 15 (36 percent) in the control group ($p < 0.05$).

The two observational studies were not reported in full.[102, 103] The lengths of followup were not clear and there was insufficient information to rate the quality of these studies. Both reported improvements, one[103] using the GCS (however, no data were reported), and one[102] using the digital symbol test (a mean 12.2-point improvement).

## Other Nontraumatic Brain Injury

### Controlled Trials

There were no trials of the use of HBOT in patients with anoxic-encephalopathic brain injury.

One controlled trial of nontraumatic brain injury has been published. In this trial, children with stable viral cerebritis resulting in altered consciousness, aphasia, spasm, and dyskinesia were randomized to HBOT or standard care.[106] A total of 92 patients were enrolled. This study was conducted in China and reported outcomes as "curative," "effective," or "ineffective." Curative was defined as disappearance of clinical symptoms and signs, normal EEG and CT; effective was defined as disappearance of some clinical signs and symptoms, better EEG and CT; and ineffective as no change. The proportion of patients found to be cured was significantly higher in the HBOT group than in controls (18 of 47 vs. 8 of 45, $p < 0.05$).[106] This study, which did not report randomization or allocation concealment methods, reported no baseline measures,

and provided no information about the timing or method (including masking) of followup assessment, was rated poor-quality.

## Observational Studies

We found three observational studies of nontraumatic brain injuries[107-109] All were rated poor-quality (see Evidence Tables 2 and 9).

**Mortality**. A poor-quality retrospective before-after study[109] reported 7 percent mortality among 136 patients with impaired consciousness after unsuccessful hanging attempts. Baseline information on patient characteristics (including comorbidities) and other treatments given is limited. No stable baseline was established, and 15 patients (11 percent) recovered before HBOT was administered. In this study, patients treated within 3-hours post-hanging had a higher recovery without neurologic sequelae than those treated later (timing not reported). It seems logical, however, that early intervention with conventional treatments may also lead to better recovery.

**Memory.** In a prospectively designed study, the Bender-Gestalt memory test (a validated test of perceptual abilities) and seven unvalidated measures were used to create a score relating to memory disturbances in patients with long-term sequelae from carbon monoxide poisoning.[108] This study includes other types of patients (not brain injury), but only data related to brain injury are reported in Evidence Table 2. How patients were selected and when the test was applied (at baseline or followup) is not reported. The study found a 5 to 10 percent improvement in the total score, with improvement in the Bender-Gestalt and story recall portions of the instrument. Interpretation of these data is not possible due to lack of important details.

**Symptoms.** Another study reported symptom improvement among children with radiation-induced necrosis.[107] Four of ten patients' symptoms improved, and another two improved initially (it is assumed that these patients regressed, but no details are given). The lack of definitions for outcomes reported, timing or baseline measurements, and masking of assessors makes this a poor-quality study.

**Clinical status.** A retrospective report of 95 cases of patients in coma, with widely varying etiologies (i.e., hanging, drowning, electrocution), reported 65 were cured (68 percent).[110] Cure was defined as consciousness and labor ability recovered, no sequelae, and the curative effect stable in followup. This study was rated poor-quality due to no baseline measures, and no details on timing of followup measures, how the assessments were made, and whether outcome assessors were masked.

## Abstracts and Conference Proceedings

Eight studies included other types of brain injury and were reported only in abstract or conference proceedings (see Evidence Table 7).[83, 111-117] Four of these studies included TBI patients along with other types of brain injuries.[83, 111, 112, 114] Because the patients are so diverse, these studies are not useful in addressing the questions posed in this report. The other four[113, 115-117] do not provide enough information about the patients included to determine if they would meet our inclusion criteria.

### Synthesis

Evidence about the effectiveness of HBOT in traumatic brain injury is conflicting (see Table 4). One trial found that HBOT reduced mortality after 1 year of followup, but survivors were much more likely to be completely or severely disabled than survivors in the control group.[89-91] The other trial found no difference in mortality after 1 year of followup.[88] There are many possible explanations for the discrepant results, including the size of the trials, the protocols used to deliver HBOT, the baseline condition of the subjects, and differences in management other than HBOT.

The quality of the controlled trials was only fair, meaning that deficiencies in the design add to uncertainty about the validity of results.[93] Neither trial of HBOT for TBI described the methods used to conceal randomization, and neither resulted in clearly similar baseline groups.

In a fair-quality observational study,[97] severely brain-injured patients had better aerobic metabolism for up to six hours after an HBOT treatment. This study did not attempt to link this physiologic improvement after HBOT sessions to measures of clinical improvement. Other observational studies reported clinical endpoints, but they used subjective methods to assess recovery and provided insufficient information to determine whether the outcomes attributed to HBOT would have been expected from the severity of injury and other prognostic characteristics of subjects.

## 2. Does HBOT improve functional outcomes in patients who have cerebral palsy?

The results for cerebral palsy are presented in Table 5 and Evidence Tables 3 and 4. Our assessments of study quality are presented in Evidence Tables 8 and 9.

### Controlled Trials

We found two controlled trials of HBOT for cerebral palsy (Evidence Table 3).[118-120] One of these studies reported outcomes in two publications.[119, 120]

**Collet, Vanasse, et al. (2001)** randomized children aged 3 to 12 years with cerebral palsy to a course of treatments with HBOT of 100 percent oxygen pressurized to 1.75 atm or a similar course of treatments with room air pressurized to 1.3 atm.[119, 120] The control treatment of 1.3 atm of room air provides approximately the same alveolar partial pressure of oxygen as 100 percent oxygen without pressurization (1 atm) given by face mask. The children were a well-defined group, with perinatal anoxia and documented cerebral palsy, motor developmental age 6 months to 4 years, and psychological development 24 months or more. Children with prenatal or antenatal causes of cerebral palsy were excluded. No concurrent interventions were allowed, and other treatments were stopped prior to the study. The primary measure of outcome was the GMFM scale, a validated measure of motor function. Eight other outcome measures were also used. All assessments were done by masked physical therapists.

Motor function improved in both groups of children. At the conclusion of 40 treatments, the mean changes in GMFM were 2.9 in the HBOT group and 3.0 in the control group; the difference was not statistically significant. Six months after initiating treatment, the mean changes were 3.4 and 3.1, respectively. This represents an increase of approximately 6 percent,

which is considered to be a meaningful improvement for a short period of time, compared to approximately 7 percent improvement on GMFM at 12 months with dorsal rhizotomy.

Cognitive outcomes were measured using neuropsychological tests, consisting of five tests with multiple components and parental assessments. Visual working memory, auditory attention, and self-control were improved in both groups. Speed of information processing, verbal working memory, and visual attention remained the same over the course of the study. The tests where improvements were seen were thought to be susceptible to a learning effect, meaning that performance may have improved with repetition of the tasks and testing procedures.

No significant differences were found on any of these outcome measures assessed at any time point, with two exceptions. When the caregivers' viewpoint was assessed with the Pediatric Evaluation of Disabilities Inventory (PEDI), the control group had significantly better mobility and social functioning. The actual data for these comparisons were not presented.

This trial was assigned a fair-quality rating. The strengths of the trial are central randomization, masked outcome assessment, and use of objective, validated outcome measures. The areas of potential concern are the allocation concealment method (sealed envelopes, which can potentially reveal the allocation), differences in groups at baseline in presumed cause and type of cerebral palsy, and a baseline difference of 9 points on the 88-point GMFM scale between the treatment and control groups.

It is unclear whether the children included in this trial are representative of children with cerebral palsy. No information is given on how the 196 children screened for inclusion in the study were identified. Of these 196 children, 43 percent of children screened were not enrolled, and 32 percent refused to participate. The baseline characteristics or GMFM scores for these children were not reported.

The **Cornell Study** (Packard 2000) was a trial in which two groups of children received HBOT, but one received treatments immediately after enrollment (n=12) and the other 6 months after enrollment (n=14).[118] The trial has not been published in a peer-reviewed journal. The children were aged 1 to 5 years, and had "moderate to severe cerebral palsy" and developmental delay of at least 33 percent in one area (areas not defined). A variety of measures (Bayley II, Preschool Language Scale [PLS], Peabody Motor Scales, PEDI) were assessed by masked physical therapists or child psychologists at baseline, 1 month, 2 months, and 5 months. However, diaries kept by unmasked parents appear to be the primary outcome measure in this study.

After 6 months, parental diaries indicated 22 percent of the subjects had major gains in skills and 44 percent of children with visual impairments (four of nine) reported improvement, but the report did not say how many of the improved children had received HBOT. Significant improvements in the PEDI score were seen initially but dissipated by 6 months. Other masked assessments and the Bayley II, PLS, and Peabody scales showed no difference between the groups.

Because a full report is not available, we could not fully assess the quality of the trial. We assigned the study a preliminary rating of poor-quality, but this rating could improve when more information about the study design becomes available. The preliminary report lacks important details regarding randomization and allocation concealment methods, baseline comparability data, and any description of the methods used to analyze results. The external validity cannot be assessed until more information about the selection and baseline characteristics of the patients becomes available.

## Observational Studies

We found three observational studies of HBOT for cerebral palsy (Evidence Table 4). The children enrolled in these studies ranged in age from under 1 year to 19 years. The HBOT protocols called for 20 treatments in all three, and the atmospheric pressure used was similar, ranging from 1.5 to 1.75 atm and oxygen from 95 to 100 percent. The duration of individual treatments varied from 20 to 30 minutes[121] up to 1 or 2 hours per day.[122]

None of these publications included an adequate description of how patients reported were selected or of the diagnostic criteria used to determine eligibility of subjects. None attempted to control for potential confounders. All used a combination of objective and subjective outcome measures, but none masked outcome assessments by using an independent rater. Finally, none of these studies described the scales used to rate outcomes in sufficient detail to assess their validity or reliability.

**Montgomery, Goldberg, et al. (1999)** is a fair-quality time series study[1] that found a mean improvement of 5.3 percent in the GMFM score after HBOT.[123] The followup period was poorly defined and could have ranged from a few days to 1 month after the treatment. Hand movement, spasticity, and parental judgments improved, but the scales used to make these assessments and the number of subjects improving were not reported. This study used different protocols at different centers and did not stratify the results based on this exposure difference. This study also excluded children with a variety of complicating factors, including recent rhizotomy and those on anti-spasticity medications.

**Chavdarov (2002)** is a poor-quality before-after study of 50 children that reported improvements of 13 percent for motor, 6 percent for mental, and 7 percent for speech abilities 2 days after HBOT.[121] Data for each scale used were not presented.

**Machado (1989)** is a retrospective study[122] of 230 patients who received HBOT for cerebral palsy. Immediately after HBOT, 218/230 (95 percent) children had reduced spasticity, based on a rating scale, but actual data were not reported. In 82 of these children followed for 6 or more months (the others were lost to followup), 62/82 (76 percent) had persisting reduction of spasticity and better motor control (data not reported). Parents reported other types of improvement, such as better balance, more attentive, and more "intelligent," with a reduced frequency of convulsions and episodes of bronchitis. Vague inclusion criteria, outcome measures, and timing of measurements make the results unreliable.[122] This study reported reduction in spasticity based on a scale (1 to 100) developed by the authors; however, it is stated that this scale was developed over time and could not have been used on all patients reported. It is not clear which patients were assessed using this scale, and the data for those who were assessed were not reported. This study was rated poor-quality.

## Abstracts and Conference Proceedings

We found five studies that were reported only in meeting abstract or conference proceeding form (Evidence Table 7). None appear to be prospective or controlled. No details on patient population were provided, interventions varied widely, and only two used objective outcome

[1] A time series is a study in which measurements are made at several times before and after treatment. In a before-after study, only one measurement is made before treatment and one measurement is made after treatment. See Figure 2.

measures. One of these two studies[124] appears to be the same as one reported above.[123] The other reported modest improvements in the GMFM immediately after HBOT[125]

## Synthesis

There is insufficient evidence to determine whether the use of HBOT improves functional outcomes in children with cerebral palsy. Observational studies (dose ranging from 1.5 to 1.75 atm) reported improvements on subjective measures and on motor function as measured by the GMFM. In the two controlled trials, however, similar improvements were seen in children who did not receive HBOT, indicating that HBOT may not be the cause of improvements seen in the observational studies.

The best evidence comes from a fair-quality randomized controlled trial, which found that HBOT at 1.75 atm and 1.3 atm of room air had a similar effect on motor function. Improvements in the GMFM over 6 months were 5 to 6 percent in both groups, which is considered significant improvement for a short period of time, and which may be compared with approximately 7 percent improvement on GMFM at 12 months with dorsal rhizotomy.

Different explanations have been offered to explain the improvement in the children who were treated with pressurized room air. The authors of the trial thought that the children in both groups improved because participation in the study provided an opportunity for more stimulating interaction with their parents. This is speculative, however, because there was no evidence to suggest that the parents and their children had less time together, or less stimulating interaction, before the study began.

Another possible explanation is that the "sham" intervention—pressurized room air—was beneficial. The trial was designed to test the efficacy of oxygen, the "active ingredient" in HBOT and in room air. At 1.3 atm, pressurized room air provides a similar amount of oxygen as unpressurized 100 percent oxygen by mask. The possibility that pressurized room air had a beneficial effect on motor function should be considered the leading explanation.

# 3. Does HBOT improve mortality and morbidity in patients who have suffered a stroke?

## Controlled Trials

Five controlled trials examined the effect of HBOT in patients with stroke.[126-131] (See Table 6 and Evidence Table 5). (One study was reported in two publications).[128, 130] Four of these were randomized,[126-128, 130, 131] and one was non-randomized.[129]

The number of patients ranged from 32 to 80. Strokes were described as ischemic,[126, 127, 131] thrombotic,[129] or vascular.[128, 130] Two trials included only acute patients who were within 24 hours of the onset of their stroke,[126, 131] another enrolled patients within 2 weeks of onset,[127] another enrolled only patients who were at least 2 months past their stroke (range 2 to 172 months, average 29.2 months) and were no longer receiving any therapy or rehabilitation,[129] and the last included patients at least 3 months post-stroke (range 3-108 months).[128, 130]

HBOT protocols varied. The dose was either 1.5 to 2.5 atm, and there was significant variation in the number and duration of treatments. The duration of each session ranged from 40 to 60 minutes, and the number of treatments ranged from a single session to 30 (see Table 6 and

Evidence Table 5). Monoplace chambers were used in three studies[126, 127, 131] and multiplace chambers in two studies.[128-130]

Control groups were active in the randomized controlled trials; three[126-128] matched the pressure of the treatment group but used room air instead of 100 percent oxygen and one used 100 percent oxygen with 1.14 atm pressure.[131] One added occupational and physical therapy to the regimen in both control and treatment group patients.[127] The non-randomized controlled trial[129] assigned 80 stroke patients to eight comparison groups with combinations of in-water or "dry" physical therapy; HBOT at different doses (1.5 or 2.0 atm); both HBOT and physical therapy; or no treatment. Patients were assigned to treatment group based on which group had an open position at the time they were assigned.

In two of the randomized trials, both patients and examiners were masked to treatment assignment.[127, 128, 130] In the other two,[126, 131] the title describes the study as double-blind, but there is no mention in the text about masking of outcome assessors (the patients received sham treatments). In the non-randomized controlled trial, the examiner, but not the patient, was masked to treatment assignment.[129]

One study reported outcomes only immediately following a single HBOT treatment,[128, 130] two measured outcomes at various points over 1 year,[126, 127] and two followed patients for 3 months.[129, 131]

**Mortality.** Only one pilot study of HBOT for stroke within 24 hours of onset of symptoms reported mortality, finding two deaths in the sham group (12.5 percent) and one in the HBOT group (6 percent) at 3 months.[131] However, the study sample size was too small to detect a difference in mortality, and the causes of death were not clearly reported.

**Neurological outcomes. Anderson, Bottini, et al. (1991),** a fair-quality, double-masked, randomized controlled trial that enrolled patients within 2 weeks of the onset of their stroke, found no significant differences between control and HBOT groups on graded neurological exams at day 5, week 6, month 4, or year 1 of followup.[127] Patients received up to 15 HBOT sessions every 8 hours at 1.5 atm. Treatment was not well accepted by patients. Twenty percent dropped out before completing the study, and 38 percent deviated from the protocol in some way. Although the differences were not statistically significant, the study was suspended early because the improvements were consistently greater in the control group.

This was the only controlled trial that reported the number of patients who were screened for inclusion. Less than half of those screened were enrolled (39/92 patients screened). Patients were excluded if they had medical contraindications for HBOT, were over age 90, had a score of less than 20 on a graded neurological exam, had deficits that were rapidly improving, or had a treatment status of "supportive care only."

**Sarno, Rusk, et al. (1972),** another fair-quality, crossover trial, found no difference in communication and cognitive outcomes in 32 stroke patients who received a single HBOT session or sham treatment.[128, 130] The main strength of this trial is that patients and outcome assessors were masked to treatment allocation, and the study used a battery of standardized tests, so the results are less likely to be affected by observer bias. The conclusions that can be drawn from this study are limited, however, because it involved only a single session of HBOT. The investigators reported that they were able to enroll only 53 percent of the original number of patients planned because of difficulty recruiting subjects. They stated that some patients refused to participate when they heard of a lack of effect of treatment. It is unclear how potential participants would have received this information before the conclusion of the study, and it raises

the possibility that patients who participated may have been different from the general population of eligible subjects.

The third randomized controlled trial, **Nighoghossian, Trouillas, et al. (1995),**[126] enrolled 34 patients within 24 hours of the onset of their stroke. Twenty-seven (79 percent) patients completed the study. When the mean neurological scores of the groups were compared, patients who received 10 HBOT treatments had significantly higher scores at 12 months on two of the three scales used (Orgogozo scale and Trouillas scale) compared to patients who were assigned to the control group. Mean scores did not differ on these scales at 6 months or on the third scale used (Rankin). Baseline Orgogozo scale scores in the HBOT group were higher, and when these differences in baseline measures were taken into account in the data analysis by comparing the mean change from baseline to 6 months, no significant differences were found on this scale. Baseline scores on the Rankin and Trouillas scales are not reported, but there was no difference in the mean change from 6 months to 12 months on either.

This study was rated poor-quality because there was a difference in the neurological scores of the groups. Because randomization and allocation concealment methods were not described, we cannot assess whether randomization was appropriately conducted, but the significant difference in baseline prognostic factors suggest that randomization failed to result in comparable groups.

**Rusyniak et al. (2003)** was a fair quality, randomized pilot study that enrolled 33 patients within 24 hours of stroke to a single session of HBOT or a sham treatment. This study assessed the proportion of patients with "good" outcome at 24 hours, based on the National Institutes of Health Stroke Scale (NIHSS), and 90 days on the NIHSS, the Barthel Index, the Modified Rankin score, and the Glasgow Outcome Scale. Good outcome was defined as a score of zero or and improvement of greater than 4 points on the NIHSS from baseline, a score of 95 or 100 on the Barthel Index, a score </= 1 on the Modified Rankin score, and a Glasgow Outcome Scale score of 5. Three patients were lost to follow up in the control group, but an intent-to-treat analysis is presented. At 24 hours 32 percent of control patients had a good outcome compared to 18 percent in the HBOT group ($p = 0.44$). At 90 days, there were no significant differences seen on any measure based on intention to treat analysis, although the proportions of patients with good outcome were higher in the control group for all measures. Using a per-protocol analysis, including only patients who completed 90 days of follow-up, the control group had significantly more patients with good outcome based on the NIHSS, Modified Rankin Scale and the Glasgow Outcome Scale.

The last controlled study, **Marroni et al. (1987),** was a non-randomized trial that used eight different treatment regimens combining HBOT with in-water or dry physical therapy compared to no treatment or in-water physical therapy alone (no HBOT).[129, 132] The number of patients in each treatment group ranged from 7 to 12; all were stable and were no longer receiving any therapy or rehabilitation. Mean outcome measure scores were plotted for each group. After 60 days, the groups of patients treated with HBOT improved by 1 and 1.8 degrees on the Kurtzke functional scale (a scale measuring walking ability and other abilities in patients with multiple sclerosis), while control groups had no improvement. Groups receiving HBOT plus physical therapy improved more, and the in-water HBOT group achieved the largest improvement. Patients were also evaluated on the Neuromotor Disabilities Evaluation Scale. This unvalidated scale, developed by the study authors, measures 10 groups of limb and system function (e.g., finger and hand function, muscular strength, walking ability) on a scale ranging from 17 (best) to 111 (worst). Over a 3-month evaluation period, mean scores in the dry HBOT groups improved by 3.1 to 3.8 degrees, and patients in control groups improved 1 degree. There were no

differences among these groups based on concurrent physical therapy or HBOT dose (1.5 or 2.0 atm). The groups receiving HBOT and concurrent in-water physical therapy improved by 7.7 degrees (1.5 atm) and 11.6 degrees (2.0 atm).

This study, which we rated poor-quality, provided no information by which to judge the comparability of the groups at baseline. For this reason it is impossible to rule out bias or confounding as explanations for the results. Because it combined HBOT with in-water physical therapy, it is impossible to determine which component was responsible for the reported improvements. Because patients were not allocated to treatments randomly, the investigators could knowingly or unknowingly assign patients with a better prognosis to a treatment they believed in. Likewise, the patients and outcome assessors were not masked to treatment; the patient could have altered their level of participation, and the outcome assessor could have knowingly or unknowingly interpreted outcomes differently, depending their beliefs about the treatment received.

## Observational Studies

There are 17 observational studies of HBOT in patients with stroke (Evidence Table 6). Nine of these are before-after studies,[108, 110, 133-139] seven are time series that measured outcomes at several points before and after treatment, [140-146] and one was a retrospective comparison of cohorts from two different hospitals. [147] The number of patients in these studies ranged from 18 to 490. HBOT treatment protocols were often adjusted according to the patient's condition, so they were not standardized either within or between studies. In general, the usual dose was between 1.5 and 2.0 atm. Duration ranged from 30 to 90 minutes, with most reporting about 15 treatments, although there was a wide range (see Evidence Table 6).

Two studies reported mortality rates; [140, 147] three measured grip strength with a dynamometer; [134, 143, 144] one performed a mental status examination, two-point discrimination, and repetitive thumb/finger movements; [144] two measured spasticity on a five-point scale; [134, 143] and one measured 33 different functions of cognition and motor ability. [137] One study[108] used a scoring system that included one standard test to measure memory (Bender-Gestalt Memory Test), but the other components of the score were not validated or well described.

In three studies,[108, 143, 144] outcomes were measured at the conclusion of HBOT treatment. Since the duration of treatment varied according to patient response, the timing of these followup measures also varied. Others followed up patients for 6 weeks, [141] every 3 months for 1 year, [148] at 6 and 12 months after treatment, [141] and 4.5 years after treatment.[146]

All of these studies had fatal flaws that led to a poor-quality rating. Only two studies established that all patients were stable at the time baseline measures were taken.[137, 139] In a before-after study, we can be confident that the results are due to treatment and not to the natural course of the illness only if the stability of their baseline condition is established clearly. This was not the case in any of these studies.

In two studies, some of the patients were observed for a long enough period to establish that they were stable.[137, 139] However, both these studies had other flaws that led to a poor-quality rating. Both used simultaneous co-interventions, such as physical therapy and biofeedback, making it impossible to determine the effects of HBOT alone. Also, they used subjective outcomes and did not mask the outcome assessors to knowledge that patients had received HBOT treatment. Masked outcome assessment is especially important when outcomes are subjective or depend on the judgment of the assessor.

As a group, the observational studies reported that between 20 and 83 percent of selected patients with stroke improved after HBOT therapy.

**Mortality.** A retrospective comparison of cohorts examined 5-year mortality rates in 65 patients who received HBOT compared to 65 patients who did not receive HBOT.[147] Thirty-two percent of the patients who received HBOT died, compared to 48 percent of those who did not receive HBOT ($p < 0.05$). There is no information on how patients were chosen for inclusion, and although patients were matched by age, sex, and time of event, significant differences in clinical history between the two groups existed (HBOT-treated patients had more hypertension, respiratory insufficiency, and vascular insufficiency of the inferior limbs). The groups were treated at two different hospitals, and it cannot be ruled out that factors other than HBOT treatment accounted for the reduction in mortality in the HBOT group. For example, 10.8 percent of patients in the HBOT-treated group received diuretics, compared with 4.6 percent of the control group patients ($p < 0.05$).

In a time series, 40 patients[149] who were at least 4 weeks from the onset of their ischemic attack and whose neurologic state was unchanged for at least 3 weeks were given HBOT treatment for 15 days, and then after a rest of 30 days, 15 more treatments if they had improved. Seven patients (17.5 percent) died. The length of the followup is unclear, so we cannot compare these results to other reports. This study was poor-quality, because stability at baseline was not established, outcomes were subjective, outcome assessors were not masked, and other interventions were given.

**Neurological examinations.** Uncontrolled observational studies found that the majority of patients showed at least some improvement, and some had extremely good results. The proportion of patients whose improvement on unspecified neurological measures was "marked," "excellent," "dramatic," or "completely cured" ranged from 6 to 64 percent. Improvement was "good" or "moderate" in 20 to 82 percent of patients. In one time series, 82.5 percent of 40 patients improved, and 11 of 15 (73 percent) of patients with aphasia improved.[149] The outcome measure used was not described. Two studies[133, 145] reported initially good responses (48 to 67 percent) during or immediately after HBOT treatment, but the improvement was maintained at followup in only 8 or 9 percent of patients. It is difficult to draw conclusions from these studies because the outcome measures are described in vague terms, and baseline measures were not presented.

**Other outcome measures.** Three studies measured grip strength using a dynamometer,[134, 143, 144] but they did not report results of all patients, only example cases. Two studies by the same author measured spasticity on a five-point scale.[134, 143] All patients also received physical therapy in addition to HBOT treatment. All patients with spasticity improved rapidly during HBOT treatment. Although the improvement was transitory, it was prolonged if physical therapy was performed in the chamber during HBOT. Improvement was maintained in "many" patients (number not specified) at 3 to 12 months of followup.

A before-after study of 50 patients measured 16 self-reported functions and 33 functions reported by physical therapists before and after HBOT therapy.[137] Following treatment, 96.7 percent of patients reported total improvement on at least one function, and 3.3 percent reported no improvement. Physical therapists reported 82 percent of patients showed good or excellent improvement on at least one function. Sixty-seven percent of patients rated the program "excellent" or "stupendous." Outcome assessors were not masked, and outcome measures were subjective and not defined.

A before-after study of 122 patients[139] reported that the degree of improvement did not appear to be related to the patient's condition at baseline, whether initiated when the patient was bedridden (55 percent improved), wheelchair bound (71 percent improved), or walking with aids (56 percent improved). Although some patients in this study were as many as 10 years post-stroke, the possibility that these results were due to bias, confounding, or both cannot be ruled out. Because the outcome measures used were subjective and the outcome assessor was not masked, the results may be biased. It is also not possible to determine if the results are due to the simultaneous physical therapy that was used in some patients.

## Abstracts and Conference Proceedings

Twelve studies of HBOT in stroke reported their results only in meeting abstracts (See Evidence Table 7). Two were controlled trials. Only one reported detailed inclusion criteria. One included subjects with other diagnoses in addition to stroke (chronic traumatic, hypoxic, and anoxic brain injuries) and did not report outcomes in stroke patients separately. One included mainly patients in critical condition in a coma. The number of patients ranged from 4 to 140. Doses ranged from 1.5 to 3.0 atm, duration from 40 to 90 minutes, and number of treatments from 1 to 80. Two studies did not report the HBOT protocol used. These studies did not provide enough information to allow quality assessment.

One of the controlled trials used a Neurological Recovery Score (improvement at 12 months HBOT vs. control, $p = 0.031$); the other reported recurrent stroke or TIA (4.8 percent TIA in HBOT vs. 5.9 percent stroke in control, p not given).

Two uncontrolled studies reported observations or results of unspecified neurological examinations. One stated that 100 percent of 18 patients with chronic traumatic, ischemic, hypoxic, and anoxic brain injuries showed motor, behavioral, personality, or cognitive gains by 40 treatments. In another, 80 percent of 140 patients with ischemic stroke improved. The other did not report the proportion of patients who improved, but reported that "nearly all" patients who responded favorably to HBOT showed a positive response to extra-intracranial arterial bypass surgery. Other uncontrolled studies measured hand grip and spasticity[143] (improvement in all four patients), recovery of consciousness (17 percent of six patients regained consciousness), and short-term memory quotient (memory quotient improved significantly from baseline, $p < 0.001$).

## Synthesis

The best available evidence shows no benefit from HBOT for stroke, but there are conflicting results from flawed controlled trials and uncontrolled studies, and no good-quality study has been conducted. Fair-quality randomized trials found no benefit in patients treated with HBOT over patients treated with pressurized room air or low-pressure oxygen. Two of these trials have limited applicability because they evaluated only a single HBOT treatment. Two flawed trials found that HBOT improved neurological outcomes on some measures. There was no pattern among these studies to suggest that any particular dose or frequency of HBOT treatment is more effective than any other.

Most observational studies reported good, and sometimes dramatic, results, but failed to prove that these results can be attributed to HBOT. Design flaws make it impossible to rule out other explanations for their results. Failure to establish that patients were stable at baseline, and

the use of other treatments, made it impossible to separate out the effects of HBOT alone. Finally, the lack of masking of outcome assessors and the use of subjective outcome measures in most studies make it impossible to rule out bias in outcome assessment. Therefore, no conclusions about the effectiveness of HBOT for stroke can be drawn from this body of evidence.

# 4. What are the adverse effects of using HBOT in brain injury, cerebral palsy or stroke patients?

Several factors are likely to affect the risk of adverse events from HBOT:

1. The condition of the patient and the criteria used to select patients for treatment
2. The precautions taken before treatment begins
3. The dose, duration, and type of equipment used to deliver HBOT affect the risk of adverse events.

These factors have been well studied in patients undergoing HBOT for some, but not all, approved indications. While it is widely agreed that these are likely to be important factors in patients treated for brain injury, the relation of these factors to the incidence and severity of adverse events has not been examined carefully in any study. In particular, we found no studies designed to determine the safety and efficacy of different doses of HBOT in this population.

## Neurological Complications

### Central Nervous System Toxicity

Central nervous system toxicity is usually considered to be the most serious complication of HBOT. In patients with FDA-approved indications for HBOT, the risk of seizure during or after HBOT is low, but increases with the dose of oxygen and the duration of treatment. In a series of 3,160 patients who underwent HBOT for various indications at two hospitals in Long Beach, California from 1967-1986, the incidence of seizure was about 1 percent.[150] The incidence was 5 percent in patients who received HBOT at 2.5 to 3 atm and was 0.5 percent (5 per 1,000) in patients who received 2 atm or less. Others cite an average risk of 1 percent to 2 percent in patients treated for less than 2 hours at doses below 3 atm.[58]

These statistics, while reassuring, come from patients who were treated for FDA-approved indications and who had no known central nervous system disease before starting treatment. There is concern that the risk of central nervous system toxicity may be higher in the setting of brain injury. There is also concern that, in addition to seizures, HBOT may cause subtler central nervous system complications, even at relatively low hyperbaric pressures. A recent series of cases published by Harch supports this view. Harch reviewed his experience in treating patients with chronic neurological conditions.[151] He found that there were three different syndromes of oxygen toxicity, defined in his study as "untoward neurological, cognitive, or constitutional signs and symptoms occurring in the setting of a course of HBOT." He described

- Eight cases of acute oxygen toxicity, including two in children. All but one of these occurred with doses of HBO of 1.75 atm or less.
- Fifteen cases of chronic oxygen toxicity, manifesting usually as neurological deterioration after a large number of HBOT dives (range 65-500+) at doses of 1.5 atm to 1.75 atm.
- Four cases of gross neurological deterioration within days of cessation of HBOT (1.5 atm, number of dives 39 to 233).

Harch notes that, in this report, which was based on a review of notes and other materials, he was not able to estimate the incidence of these complications. His impression was that reducing the treatment time from 90 to 60 minutes reduced the incidence of these complications. It was also his impression that, contrary to conventional wisdom, all three of these syndromes could result in long-term detrimental effects.

The few data that are available from controlled trials and cohort studies reinforce the idea that the risk of seizure may be higher in patients with brain injuries than in others. In Rockswold et al., which used 1.5 atm, two of 84 patients (12 percent) had seizures. HBOT was discontinued in another patient whose GCS motor score decreased by 1 point "without apparent explanation." Seizures were reported in four patients in three other studies, including one status epilepticus that lasted 12 hours,[88, 96, 98] but the incidence of seizures was not calculated. No seizures were reported in the two trials of HBOT for children with cerebral palsy. Two of the observational studies reported the occurrence of seizures, but neither calculated the incidence. There were no reports of seizure in any study of stroke, and no evidence that neurological deterioration was more likely to occur in patients undergoing HBOT than in controls.

No study of HBOT for brain injury, cerebral palsy, or stroke has been designed to identify the chronic neurologic complications described by Harch. In a recently published trial of HBOT for acute carbon monoxide poisoning, however, patients treated with HBOT had worse long-term neurologic outcomes than those treated with normobaric oxygen.[68] This result should not be generalized to patients who are treated for brain injuries, for which the long-term neurologic outcome has only been studied for severely injured, comatose patients.

## Pulmonary Complications

HBOT can cause aspiration, which may cause pneumonia or increased oxygen requirements. Patients who have a reduced level of consciousness and those who have gastroesophageal reflux have a higher risk of aspiration. Aspiration results when swallowed air leads to distension of the stomach and, consequently, regurgitation of stomach contents into the pharynx, where they may be drawn into the trachea and lungs.

Paralysis, lack of control, or weakness of the muscles involved in the gag reflex or swallowing are also risk factors for aspiration. Placing a feeding tube into the stomach can reduce the risk of aspiration. This prevents distension of the stomach and reduces the risk of regurgitation.

Pulmonary complications were relatively common in the trials of brain-injured patients. In the Artru trial, which used 2.5 atm, treatment was stopped in 35 percent (11/31) of sessions due to pulmonary symptoms.[88] No further information was provided about the severity of these complications, their duration, or whether treatment was restarted later. The chamber type was not reported. In the Rockswold trial, which used 1.5 atm, HBOT had to be permanently stopped

because of adverse effects in 10/84 (12 percent) patients. The reasons for withdrawal of therapy were not described clearly. Pulmonary complications (increasing FiO2 requirement and/or infiltrates detected on chest x-ray) were described as the most frequent complication, but the number of cases was not reported.

There are no reliable data on the incidence of aspiration in children treated for cerebral palsy with hyperbaric oxygen. No cases of aspiration were reported in the Collet and Cornell trials.[118-120] Nuthall reported two cases of children with cerebral palsy who, after HBOT, had acute respiratory failure requiring ICU admission.[152] The first child underwent two HBOT dives at 1.75 atm. Between the two dives he was fed a meal, which he aspirated during the second dive. The authors noted that, during the hyperbaric treatments, the child's head was completely enclosed by a vinyl hood with latex seals around his neck for the delivery of oxygen. The second child was thought to have suffered an air embolism.

In response, Harch, Deckoff-Jones, and Neubauer wrote a letter to the editor of the journal *Pediatrics.* They noted that the incidence of pulmonary aspiration in practice is unknown, but, between them, they had "logged over 35,000 treatments on brain injured children without a single case of primary aspiration or air embolism."[153]

## Ear Problems

HBOT can cause pain, rupture, or hemorrhage in the ear. The most common symptom is a feeling of pressure and pain in the eardrum. Alert patients can prevent these symptoms by swallowing and other maneuvers (similar to what one does when the pressure in the cabin of a plane increases during a descent.) In children and other patients who cannot perform these maneuvers, myringotomy (making a hole in the eardrum) can prevent the symptoms.

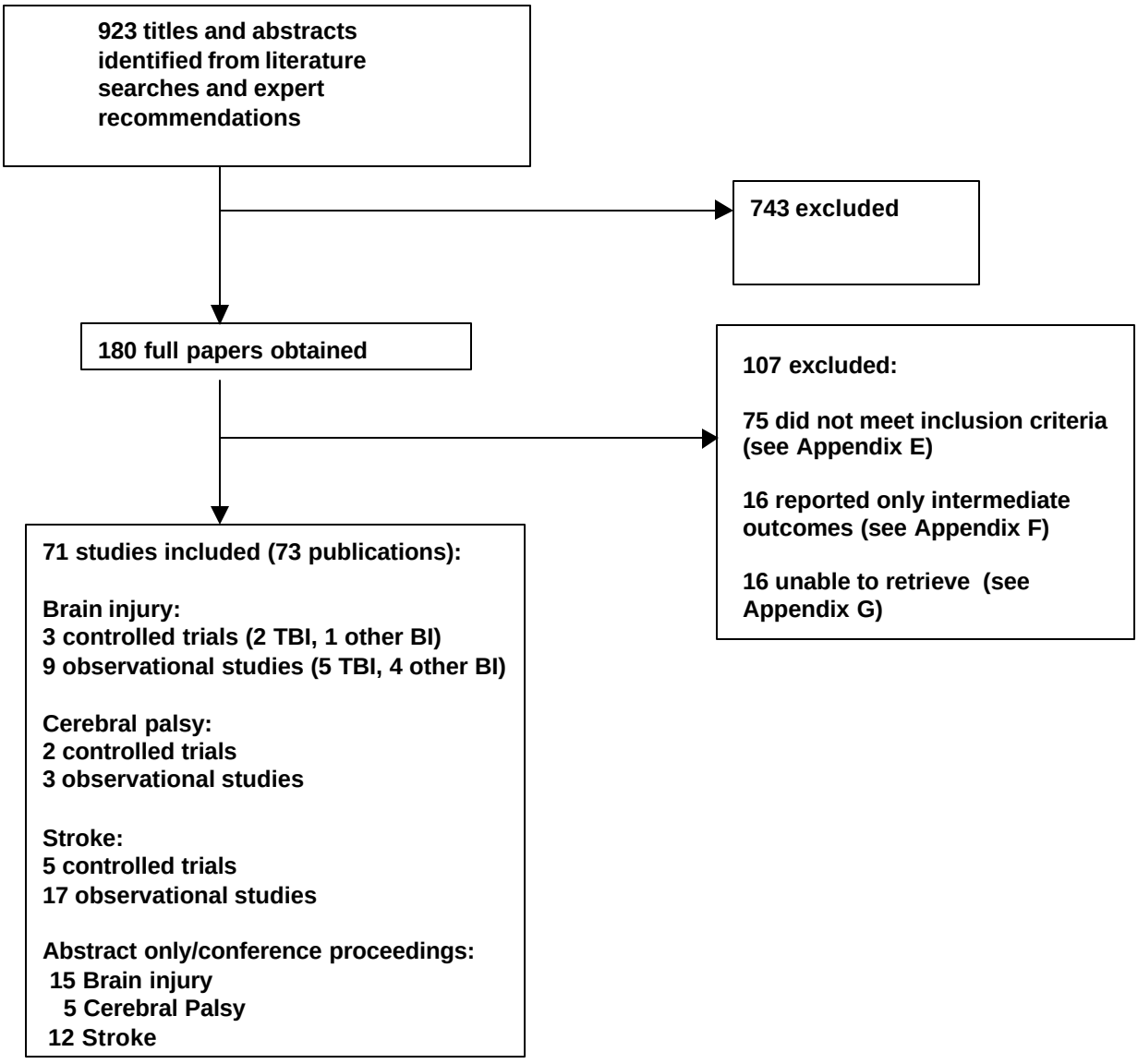
In acute TBI, the Rockswold study, which used 1.5 atm, reported that after two of 38 patients (5 percent) had hemotympanum, prophylactic myringotomies were performed on the last 46 patients enrolled in the HBOT arm. [89-91] A monoplace chamber was used in this study.

The controlled trial of HBOT for cerebral palsy (Collet et al) provided the best data on the frequency of ear problems in children. In that trial, 47 percent of children assigned to HBOT and 22 percent of children assigned to compressed air developed ear problems due to compression. Both multiplace and monoplace chambers were used in this study, but the data were not stratified by this variable. In the Cornell study (using 1.5 atm pressure), 35 percent of patients experienced ear problems related to pressure.[118] Chamber type was not reported in this study. Ear problems were not reported in the controlled studies of stroke patients, and one uncontrolled study reported ear problems in 6 percent of 122 patients, with 1 percent requiring myringotomy.[139]

## Quality of Evidence about Adverse Events

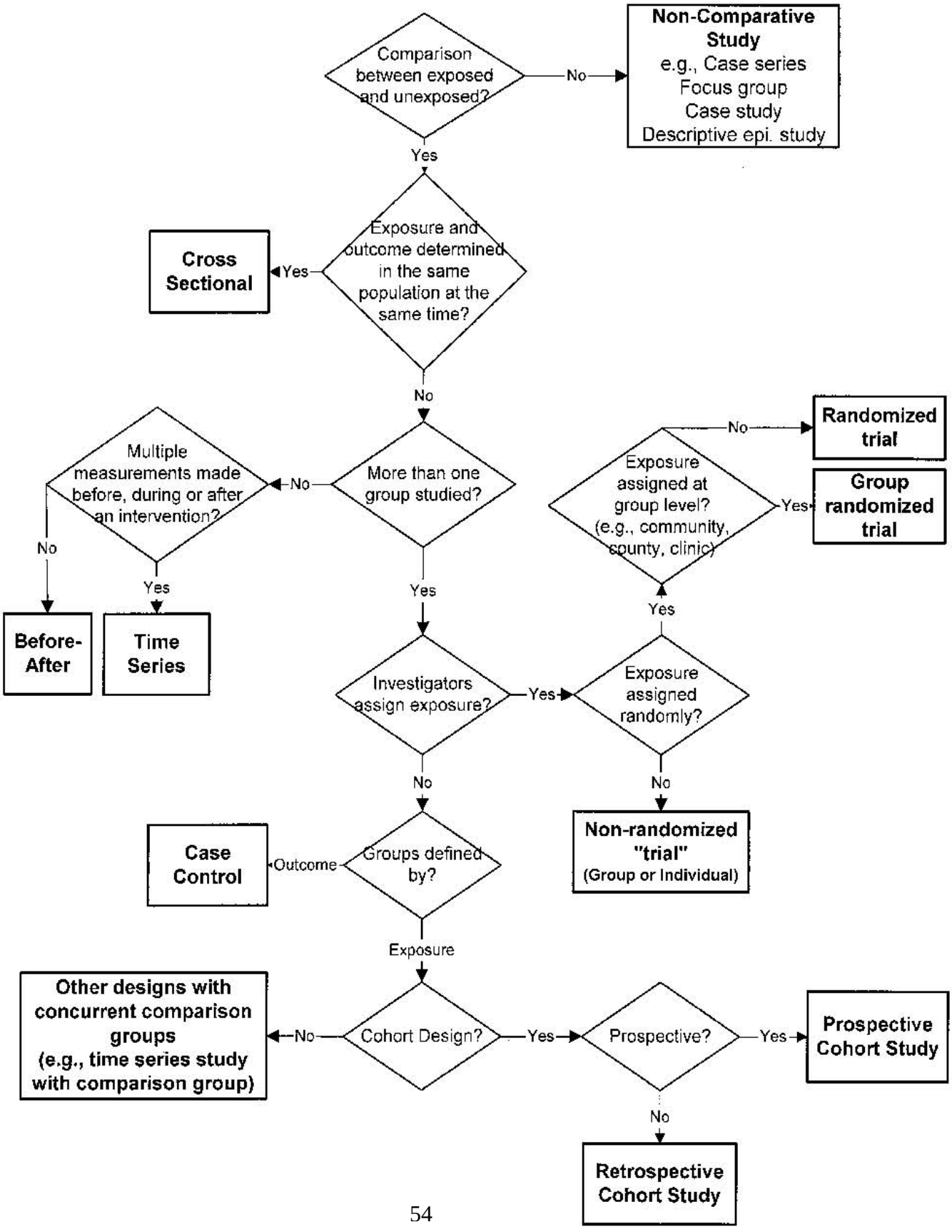
Except as noted above, the quality of evidence about adverse events was almost universally poor in the studies we reviewed. Some studies reported overall rates of withdrawal, but did not specify whether patients withdrew from the HBOT or the control group. Most did not state the reasons for withdrawal. None of the observational studies described a protocol for detecting and classifying adverse effects. Without such a protocol, event rates are almost certain to be underestimated.

## Figure 1. HBOT Literature search results




TBI = traumatic brain injury; BI= brain injury

## Figure 2. Study Design Algorithm*






*Zaza S, Wright-De Aguero LK, Briss PA, et al. Data collection instrument and procedure for systematic reviews in the guide to community preventive services. Am J Prev Med 2000;18(1 Suppl):44-74.

## Table 4. Controlled trials of HBOT in brain injury

| Study, population, n | HBOT Protocol;Control | Results | Quality Rating |
|---|---|---|---|
| ***Traumatic brain injury*** | | | |
| Artru, 1976[88]<br>France; Patients with head injuries and in a coma;<br>31 HBOT, 29 control | 2.5 atm x 60 minutes x 10 days of treatment alternating with 4 days off until patient regained consciousness or died.<br><br>Control: Standard treatment | No significant difference on any comparison (persistent coma at 1 month, consciousness recovery rate at 1 month, death rate at 1 month, death rate at 1 year, mean duration of coma, except in 1 of 9 subgropus: patients less than age 30, not reacting in an adapted manner to painful stimuli, and not operated on)<br>n=9<br>HBOT, 9 control.<br><br>Persistent coma at 1 month:<br>22% (HBOT); 78% (control); p<0.03<br><br>Independent in daily activities at 1 year among survivors:<br>45% (HBOT); 41% (control) | Fair |
| Rockswold, 1992,[90] 1994[91]<br>Minnesota; severe head injury at one institution, admitted 1983-1989.<br>Total GCS score of 9 or less for at least 6 hours; 84 HBOT, 84 control | 1.5 atm x 60 minutes every 8 hours x 2 weeks or until the pt was brain dead or could consistently follow simple commands. Average 21 treatments per patient.<br><br>Control: standard intensive neurosurgical care, all patients received phenytoin. | Mortality at 12 months:<br>14/84 (17%) (HBOT); 26/82 (32%) (control)<br>$p$ = 0.04<br><br>Favorable outcome at 12 months (GCS score of 1 or 2)<br>44/84 (52%) (HBOT); 44/82 54%) (control)<br>$p$ = 0.99 | Fair |
| ***Other brain injury*** | | | |
| Jianhua, 1995[106]<br>China; children (aged 1 to 11 years) with viral cerebritis;<br>47 HBOT, 45 control | 1.8-2.0 atm x 90 minutes once daily x 10 days.<br><br>Control: supportive therapy, including drugs naofukang, naofuxin. | HBOT group: 18/47 (38%) curative, 25/47 (53%) effective, 3/47 (6%) ineffective (1 missing?).<br>Control group: 8/45 (18%) curative, 20/45 (44%) effective, 17/45 (38%) ineffective.<br>HBOT vs control: % curative $p$ < 0.05, % effective p > 0.05, % ineffective $p$ < 0.001. | Poor |

GCS=Glasgow Coma Scale; GOS=Glasgow Outcomes Scale; atm=atmospheres ; NS=non-significant; ICP=intracranial pressure; CT=comuterized tomography

## Table 5. Controlled trials of HBOT in cerebral palsy

| Study, population, n | HBO Protocol (Type of chamber) Control | Results | Quality rating |
|---|---|---|---|
| Collet, 2001[119]<br>Canada<br><br>Children with cerebral palsy with history of hypoxia in perinatal period, age 3-12 years, motor development age of 6 months to 4 years, and psychological development age 24 months or more. | 100% oxygen at 1.75 atm x 60 minutes x 40 sessions. Sessions 5 days/week x 8 weeks.<br>(Chamber type not given)<br><br>Control: Room air at 1.3 atm x 60 minutes x 40 sessions. Sessions 5 days/week x 8 weeks. | Change in Global Gross Motor Function Measure<br>Post-intervention (after 40 treatments):<br>HBOT: 2.9 (1.9, 3.9)<br>Control: 3.0 (2.1, 3.9)<br>*p* = 0.54<br><br>At 3 months:<br>HBOT: 3.4 (2.2, 4.5)<br>Control: 3.1 (2.2, 4.1)<br>*p* = 0.97<br><br>Secondary outcome measures: NS between groups (including other measures of functional status and neuropsychiatric assessments) | Fair |
| Packard, 2000[118]<br>New York<br><br>Children age 15 months to 5 years, with CP secondary to prenatal insults, premature birth, birth asphyxia, and post-natal hemorrhage. Criteria for enrollment were age between 1 and 5 years, moderate to severe CP, no evidence of brain malformation, developmental delay of at least 33% in one area, and no active seizures for the previous 6 months. | 1.5 atm x 60 minutes twice daily x 40. Five days per week for 4 weeks.<br>(Chamber type not given)<br><br>Control: Delayed HBOT treatment 6 months after first group.<br><br>T1= baseline, T2=1month after baseline (Group 1 treated, Group 2 not treated), T3=5 months after baseline, T4=6months after baseline (Group 1 5 months post-treatment, Group 2= just treated). | Blinded Assessments:<br>No statistical difference in change scores on any blinded assessments (change in Peabody scores for T2 minus T1 and T4 minus T3; change in Bayley II and PLS scores for T3 minus T1), *p* values not given.<br>*PEDI Results:* Improved scores on mobility sub-domains of PEDI for time period T2 minus T1 in favor of immediately treated group ($p<0.05$), trend favoring recently treated delay group for time period T4 minus T3 ($p<0.058$).<br>***Parental diaries:***<br>83% of parents noted a marked improvement in mobility, however no comparison between groups given.<br>Improved vision:<br>4/9 (44%) children with cortical visual impairment had improvement in vision noted by families, vision therapists and ophthalmologists. | Poor |

## Table 6. Controlled trials of HBOT in stroke.

| Study, population, n | HBO Protocol; Control | Results | Quality Rating |
|---|---|---|---|
| Anderson, 1991[127]<br>Minnesota; patients with ischemic cerebral infarction; 20 HBOT, 19 control. | 100% oxygen at 1.5 atm x 1 hour every 8 hours x 15 treatments. Vitamin E 400 units given with each HBOT.<br>Control: Room air at 1.5 atm x 1 hour every 8 hours x 15 treatments.<br>Both groups received standard ICU plus physical and occupational therapy. | Average graded neurological exam scores<br>Baseline 44.6 (control), 45.5 (HBOT):<br>Day 5: 38.5 (control), 43.8 (HBOT) $p$ = 0.54<br>Week 6: 28.3 (control), 38.5 (HBOT) $p$ = 0.25<br>Month 4: 25.6 (control), 34.5 (HBOT) $p$ = 0.33<br>Year 1: 25.8 (control), 31.4 (HBOT) $p$ = 0.53 | Fair |
| Sarno JE, 1972,[128] and Sarno MT, 1972[130]<br>New York; patients with vascular stroke at least 3 months post-stroke.<br>32 (all received both HBOT and control; order randomized) | 100% oxygen at 2.0 atm x 1.5 hours x 1 session.<br><br>Control: 10.5% oxygen at 2.0 atm x 1.5 hours x 1 session. | Communication baseline done 24 hours prior to exposure, and immediately after HBOT treatment. No significant effect on any measure. | Fair |
| Rusyniak, 2003[131]<br>Indiana; patients presenting within 24 hours of ischemic stroke; 17 HBOT, 16 control | 100% oxygen at 2.5 atm x 1 hour<br><br>Control: 100% oxygen at 1.14 atm x 2 hour | No difference in proportion with good outcome on NIHSS at 24 hours (HBOT 18%, control 31%, p=0.44)<br><br>90 days: No difference based on intention to treat using Barthel Index, Modified Rankin score, GOS, or NIHSS.<br>Control group significantly higher proportion with "good" outcome on Modified Randkin score, GOS and NIHSS by per protocol analysis. | Fair |

## Table 6. Controlled trials of HBOT in stroke.

| Study, population, n | HBO Protocol; Control | Results | Quality Rating |
|---|---|---|---|
| Nighoghossian, 1995[126]<br>France<br>Patients with ischemic stroke in middle cerebral artery confirmed by CT and seen within 24 hours of onset; 17 HBOT, 17 control | 100% oxygen at 1.5 atm x 40 minutes daily x 10 treatments.<br><br>Control: Room air at 1.5 atm x 40 minutes daily x 10 treatments. | Pretherapeutic and posttherapeutic differences (HBOT-Control)<br>No significant differences on Orgogozo scale, Trouillas scale, or Rankin scale at 6 months or 1 year | Poor |
| Marroni, 1987[129], 1988[132]<br>Italy<br>Stabilized stroke patients no longer undergoing any form of therapy or rehabilitation who had a stroke from 2 to 172 months earlier (average 29.2 months).<br>80 total | Group C1: 2.0 atm x 60 minutes x 30 sessions; Group C2: Same as C1 at 1.5 atm; Group D1: in-water rehab + HBOT 2.0 atm x 60 minutes; Group D2: Same as D1 at 1.5 atm; Group E1: 30 simultaneous, 60-minute HBOT + 40-minute in-water rehab sessions at 2.0 atm; Group E2: Same as E1 at 1.5 atm. Control*:* Group A: No treatment, Group B: 30 in-water physical therapy sessions x 40 minutes. | All dry HBOT groups showed greater improvement in their motor ability, but no clear-cut difference could be observed among the 4 groups that scored improvements of from 3.1 to 3.8 degrees. HBOT 1.5 atm rehab group reached 8.1 degrees 1 month after treatment, leveling off to 7.7 at 3 months, and the 2.0 atm HBOT rehab group showed an 11.6 degree improvement still present 3 months after treatment. | Poor |

# Chapter 4. Conclusions

In this review, we sought to answer the question: how strong is the overall evidence regarding hyperbaric oxygen for brain injury, cerebral palsy, and stroke, and what are the logical next steps?

## 1. Does HBOT improve mortality and morbidity in patients who have traumatic brain injury and anoxic ischemic encephalopathy?

### Traumatic Brain Injury

Overall, the two available fair-quality trials provide fair evidence that HBOT might reduce mortality or the duration of coma in severely injured TBI patients. However, in one of these trials, HBOT also increased the chance of a poor functional outcome. Therefore, they provide conflicting evidence to determine whether the benefits of HBOT outweigh the potential harms.

Although they are cited frequently, the case series and time-series studies of HBOT for TBI patients had serious flaws. There were no high-quality studies of the use of HBOT to improve function and quality of life in patients with chronic, stable disabilities from TBI. The most important gap in the evidence is a lack of a good quality time-series study or controlled trial of the effects of HBOT on cognition, memory, and functional status in patients with deficits due to mild and moderate chronic TBI.

Studies of the effects of HBOT on ICP levels also had mixed results. HBOT may be effective in reducing elevated ICP in some acute TBI patients, but rebound elevations higher than pretreatment levels can occur. The clinical benefit of the ICP lowering and the harm attributable to the rebound elevations are unclear. Without further delineation of the patient or treatment factors that may be associated with successful lowering of ICP, the current evidence is insufficient to determine whether the overall effect of HBOT on ICP is beneficial or harmful.

### Other Brain Injury

We did not identify any good or fair-quality studies of HBOT for anoxic-ischemic encephalopathy. We found one randomized controlled trial and five before-after studies of patients with various kinds of nontraumatic brain injuries. All of these studies were poor-quality. The controlled trial lacked details regarding the subjects' recruitment and baseline characteristics and the methods used to randomize subjects and measure outcomes. All five before-after studies lacked objective outcome measures and masked assessment, and timing of baseline and followup measures was not clear.

## 2. Does HBOT improve functional outcomes in patients who have cerebral palsy?

There is insufficient evidence to determine whether the use of HBOT improves functional outcomes in children with cerebral palsy to a greater degree than pressurized room air. In the

only controlled trial, HBOT and pressurized room air resulted in similar, clinically significant improvements in motor function. Two fair-quality observational studies (one time-series, one before-after) found improvements in functional status comparable to the degree of improvement seen in both groups in the controlled trial. The data suggest that, at least temporarily, HBOT and pressurized room air improved caregiver burden.

## 3. Does HBOT improve mortality and morbidity in patients who have suffered a stroke?

The best evidence from three fair-quality RCTs showed no benefit to HBOT on neurological outcomes, but external validity is limited by protocol (one treatment only) in two studies, and by low response rate and adherence to treatment in another. No controlled trial measured mortality. Results from poor-quality controlled trials and observational studies were more positive, but it is not possible to rule out bias and confounding as explanations for their results.

## 4. What are the adverse effects of using HBOT in these conditions?

Ear problems and pulmonary complications were relatively common in patients undergoing HBOT for brain injury. Evidence about the type, frequency, and severity of seizure and other manifestations of oxygen toxicity is inadequate. In observational studies, reporting of adverse effects was limited, and no study was designed specifically to assess adverse effects. The frequency and severity of complications in community practice has not been studied.

# Chapter 5. Future Research

## 1. Outcome Studies

We identified several barriers to conducting controlled clinical trials of HBOT for brain injury and particularly cerebral palsy. Strategies can be developed to conduct good-quality studies to overcome each of these barriers.

*Lack of agreement on the dosage* of HBOT and the duration of treatment is an important barrier to conducting good-quality clinical studies. Oxygen, the "active ingredient" in HBOT, is fundamentally a drug. For new drug therapies seeking approval by the Food and Drug Administration, the dosage and duration of treatment must be determined in carefully designed dose-ranging studies before definitive studies demonstrating clinical efficacy can be started.

Good-quality dose-ranging studies of HBOT for brain injury can be done, based on the model used by pharmaceutical manufacturers and the FDA. It is likely that the dosage of HBOT needs to be individualized based on the patient's age, clinical condition, and other factors. This is the case for many other drugs and does not pose an insurmountable barrier to designing dose-finding trials. In fact, the need to individualize therapy makes it essential to base the design of long-term studies of clinical outcomes on the results of dose-ranging studies.

*Lack of independent, reliable data on the frequency and severity of adverse events.* Uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT. The case against HBOT is based on the reasoning that, *because HBOT may be harmful, it must be held to the highest standard of proof.* A corollary is that, if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its efficacy can be lowered.

This reasoning is consistent with the views of most clinicians and with the theoretical underpinnings of rational decision-making (i.e., utility theory). Consider a treatment that has been proven to be harmless and without cost. If there is a 1 percent chance that the treatment works, a rational decisionmaker would try it—there is a potential gain and no potential loss. On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it.

A strategy for identifying common adverse events associated with the use of HBOT in each clinical area (brain injury, cerebral palsy, and stroke) should be developed, with the goal of identifying the general level of risk involved. Important potential adverse effects of a drug may not be known or suspected before a study is conducted. For this reason, good-quality studies of adverse effects must be planned to assess harms that may not be known or even suspected. The most common strategy is to use a standard template of several dozen potential adverse effects affecting each organ system. Other characteristics of a good study of adverse events include a clear description of patient selection factors, independent assessment of events by a neutral observer, and the use of measures for the severity (rather than just the occurrence) of each event.

*Relevant outcome measures.* Some of the most important outcomes of treatment are difficult to measure. Previous trials have relied primarily on standardized measures of motor and neuro-cognitive dysfunction. These measures do not seem to capture the impact of the changes that parents perceive. An apparently "small" improvement can have a big impact on caregivers.

Caregivers' perceptions should be given more weight in evaluating the significance of objective improvements in a patient's function. Unfortunately, studies have not consistently measured caregiver burden, or have assessed it only by self-report. Studies in which the

caregivers' burden was directly observed would provide much stronger evidence than is currently available about treatment outcome.

*Patients' unwillingness to be assigned to a placebo or sham treatment group* is another barrier to conducting controlled trials. One funded trial of HBOT that incorporated a true placebo group had to be cancelled because patients were unwilling to undergo sham HBOT treatments for several months.

Whether placebo-controlled trials are necessary to evaluate HBOT has received a great deal of attention in discussions about HBOT. Participants on all sides of this debate make the assumption that an "evidence-based" approach implies devotion to double-blind, placebo-controlled trials without regard to practical or ethical considerations. This assumption is false. Double-blind, placebo-controlled trials are the "gold standard" for government regulators overseeing the approval of new pharmaceuticals, but not for clinical decision-making or insurance coverage decisions. Evidence-based clinical decisions rely more heavily on comparisons of one treatment to other potentially effective therapies, not to placebos.

Several alternatives to the double-blind, placebo-controlled trial can be used to examine effectiveness. One approach is to compare immediate to delayed treatment with HBOT, as was done in the Cornell trial. Another is to design a trial in which patients are randomly assigned to several alternative HBOT regimens. Because of uncertainty about the dosage and duration of treatment, such a trial would be preferable to a trial that offered a choice between one particular regimen and no treatment at all. It is also easier to incorporate a sham therapy arm in such a trial: patients may be more willing to enter a trial if they have a 10% or 20% chance of being assigned to sham treatment instead of a 50% chance. Other alternatives to a placebo include conventional physical, occupational, and recreational therapy, or another alternative therapy, such as patterning.

The Collet trial of HBOT for cerebral palsy[119, 120] has important implications for the design of future research. In that trial there was a clinically significant benefit in the control group. Debate about the trial centers largely on how the response in the control group should be interpreted. The trial investigators believe that the beneficial effect was the result of the psychological effect of participating in the trial and extra attention paid the children in and out of the hyperbaric chamber. Alternatively, the slightly pressurized air (that is, "mild" hyperbaric oxygen) may have caused the improvement. A third possibility is that the slightly increased oxygen concentration, not the pressure per se, was responsible for the benefit.

A trial that could sort out which of these explanations was true would have a major impact on clinical practice. Such a trial might compare (1) room air under slightly elevated pressure, delivered in a hyperbaric chamber, to (2) elevated oxygen concentration alone, delivered in a hyperbaric chamber, and to (3) an equal amount of time in a hyperbaric chamber, with room air at atmospheric pressure. From the perspective of a neutral observer, the third group is not a "sham" but rather an attempt to isolate the effect of the social and psychological intervention cited by the investigators.

In addition to improved design, future trials of HBOT need better reporting. This would aid the interpretation and application of research results. Two types of information are essential: a clear description of the research design, particularly of the control and comparison groups, and a detailed description of the patient sample.

## 2. Studies of Diagnostic Tests and Intermediate Outcome Measures

*An independent, critical assessment of the body of animal experiments and human case studies supporting the "idling neuron" theory of brain injury and recovery should been done.* A large body of studies supports the theory underlying the use of HBOT, but the interpretation of these studies is also disputed. Most of these studies use experimental animal models of brain injury and are designed to support the hypothesis that HBOT redirects blood flow to, and promotes recovery and growth of, "idling neurons" at the border of the damaged brain tissue.

There is sharp disagreement in the medical literature over the validity of these experimental models. One major issue is the significance of improvements in patterns of cerebral blood flow. The principle that redirecting flow toward ischemic areas can help damaged tissue recover is well established in cardiology. However, in critical care generally, drugs and maneuvers that redirect flow to ischemic organs (e.g., brain and kidney) do not always improve recovery at the cellular level. For this reason, improved blood flow must be linked to other measures of cellular and organ recovery.

*HBOT for brain injury is not likely to gain acceptance in routine clinical use until a clinical method of assessing its effectiveness in the individual patient is validated.* Specifically, the diagnostic value of SPECT scans and of other intermediate indicators of the effects of HBOT should be examined in good-quality studies. Like all other diagnostic tests, SPECT scans have a measurable false positive and false negative rate in relation to clinical outcomes. Controlled trials are not needed as the ideal study design to measure the accuracy of a diagnostic test. Rather, a longitudinal cohort study in which all patients undergo scans as well as standardized followup tests would be a feasible and ideal approach.

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## Evidence Table 1. Brain injury controlled trial data

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Control | Randomized? |
|---|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | | |
| Artru 1976[88] France (Fair) | Patients with head injuries and in a coma. | 2.5 atm x 60 minutes x 10 days of treatment alternating with 4 days off until patient regained consciousness or died. Control group received standard therapeutic measures. (Type of chamber not specified) | Standard therapeutic measures were the same in both groups. | Yes |



HBOT=hyperbaric oxygen therapy; GCS=Glasgow Coma Scale; GOS=Glasgow Outcomes Scale; atm= atmospheres; NS= non-significant; ICP=intracranial pressure; CT=computerized tomography; EEG=electroencephalogram

## Evidence Table 1. Brain injury controlled trial data (continued)

| Author, year, location (Quality) | Baseline differences between groups | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | | |
| Artru 1976[88] France (Fair) | No information on factors other than those on which they matched participants. Severity of coma (based on Jouvet scale) was 9.39 for HBOT and 9.59 for control group (NS). Types of brain lesions similar except acute subdural hematoma (7 in HBOT and 3 in control group). Age similar (29.9 HBOT, 29.7 control). | 31 HBOT<br>29 control | Mortality rate, coma/conscious. | Mortality assessed at 1 month and 1 year, coma/conscious assessed at 1 month. |



HBOT=hyperbaric oxygen therapy; GCS=Glasgow Coma Scale; GOS=Glasgow Outcomes Scale; atm= atmospheres; NS= non-significant; ICP=intracranial pressure; CT=computerized tomography; EEG=electroencephalogram

## Evidence Table 1. Brain injury controlled trial data (continued)

| Author, Year, Location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | |
| Artru 1976[88] France (Fair) | *Persistent coma at 1 month:*<br>32% (HBOT); 38% (control)<br>*Consciousness recovery rate at 1 month:*<br>42% (HBOT); 28% (control)<br>*Death rate at 1 month:*<br>26% (HBOT); 34% (control)<br>*Death rate at 1 year:*<br>48% (HBOT); 55% (control)<br>*Mean duration of coma:*<br>28.2 days (HBOT); 32.7 days (control)<br>Independent in daily activities at 1 year among survivors:<br>45% (HBOT); 41% (control)<br>*p* = NS for all comparisons<br><br>*Subgroup 5 (* n = 9 HBOT, 9 control; patients less than age 30, not reacting in an adapted manner to painful stimuli, and not operated on):<br>*Persistent coma at 1 month:*<br>22% (HBOT); 78% (control); p < 0.03<br>*Consciousness recovery rate at 1 month:*<br>67% (HBOT); 11% (control); p < 0.03<br>*Death rate at 1 month:*<br>11% (HBOT); 11% (control)<br>*Death rate at 1 year:*<br>11% (HBOT);44% (control); p = 0.15 | Major medical reason for interruption was development of pulmonary symptoms indicating an intolerance to HBOT: polypnea with expiratory dyspnea, cyanosis at exit of chamber, and reduced oxygen saturation value. Treatment interrupted in 5 cases where the intolerance was severe enough to suggest impending hyperoxic pneumonia. Treatment interrupted in 6 others with severe pulmonary infections for fear of aggravating the lesions. | Severe chest injury or open brain wounds were excluded. Inclusion in this study depended on availability of the HBOT chamber. All assessed by same examiner at entry. |



HBOT=hyperbaric oxygen therapy; GCS=Glasgow Coma Scale; GOS=Glasgow Outcomes Scale; atm= atmospheres; NS= non-significant; ICP=intracranial pressure; CT=computerized tomography; EEG=electroencephalogram

## Evidence Table 1. Brain injury controlled trial data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Control | Randomized? |
|---|---|---|---|---|
| Rockswold 1985,[89] 1992,[90] 1994[91] Minnesota (Fair) | Patients with severe head injury at one institution, admitted 1983-1989.Total GCS score of 9 or less for at least 6 hours. | 1.5 atm x 60 minutes every 8 hours x 2 weeks or until the patient was brain dead or could consistently follow simple commands. Average 21 treatments per patient. (Monoplace) | All patients received intensive neurosurgical care, according to standard medical practice covering stabilization in the emergency department, surgical management, medical treatment and the management of intracranial pressure. However, HBOT patients received closer ICP monitoring. All study patients received phenytoin. | Yes |
| ***Studies of other brain injury*** | | | | |
| Jianhua 1995[106] China (Poor) | Children (age 1-11 years) with viral cerebritis, stable illness but with disturbance of consciousness, aphasia, spasm and dyskinesia, etc. inpatients with confirmed cerebritis. | 1.8-2.0 atm x 90 minutes once daily x 10 days. | Control group received supportive therapy, including drugs naofukang, naofuxin. | Yes |

HBOT=hyperbaric oxygen therapy; GCS=Glasgow Coma Scale; GOS=Glasgow Outcomes Scale; atm= atmospheres; NS= non-significant; ICP=intracranial pressure; CT=computerized tomography; EEG=electroencephalogram

## Evidence Table 1. Brain injury controlled trial data (continued)

| Author, year, location (Quality) | Baseline differences between groups | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| Rockswold 1985,[89] 1992,[90] 1994[91] Minnesota (Fair) | Small differences in proportion with operable mass lesions, multiple trauma, elevated ICPs and "poor outcome BAEPs (Brainstem Auditory Evoked Potentials) and SSEPs (Somatosensory Evoked Potentials ) | 84 HBOT, 84 control | ICP, mortality, GCS, favorable outcome (GCS score 1-2). | Assessed at baseline and comparisons were done at 12-month exam. Other followup assessments at 6 and 18 months. |
| ***Studies of other brain injury*** | | | | |
| Jianhua 1995[106] China (Poor) | No statistical test performed, but baseline characteristics reported, appear similar. | 47 HBOT 45 control | Curative: disappearance of clinical symptoms, signs, normal EEG and CT; effective: disappearance of some clinical signs and symptoms, better in EEG and CT; ineffective: no change in clinical symptoms through examination of EEG and CT. | Not reported. |

HBOT=hyperbaric oxygen therapy; GCS=Glasgow Coma Scale; GOS=Glasgow Outcomes Scale; atm= atmospheres; NS= non-significant; ICP=intracranial pressure; CT=computerized tomography; EEG=electroencephalogram

## Evidence Table 1. Brain injury controlled trial data (continued)

| Author, Year, Location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Rockswold 1985,[89] 1992,[90] 1994[91] Minnesota (Fair) | Mortality at 12 months:<br>14/84 (17%) (HBOT)<br>26/82 (32%) (control)<br>*p* = 0.04<br><br>Favorable outcome at 12 months (independent with or without disability, as assessed by masked neurologist)<br>44/84 (52%) (HBOT)<br>44/82 (54%) (control)<br>*p* = 0.99<br>Results at 6 and 18 months not reported, but stated NS.<br><br>Mean peak ICP<br>No significant difference in peak ICP values between HBOT (all) and control (t = 0.92).<br>HBOT (no myringotomy) subset (37 patients): 33.0 +/ 20.6 (p<0.05 compared to HBOT + myringotomy group)<br>HBOT + myringotomy subset (42 patients): 22.1 +/- 11.7<br>Control: (77 patients): 30.3 +/ 24.3 (*p* <0.05 compared to HBOT + myringotomy group) | Most frequent complication was pulmonary, increasing FiO2 requirement and chest x-ray infiltrates. In 10 patients, HBOT had to be permanently stopped. 2 patients had isolated generalized seizure. 2 had hemotympanum. One patient's family requested HBOT be discontinued. | Assessors at 6, 12 and 18 months were unaware of patient's treatment group. Bilateral myringotomies performed in the last 46 of the 84 patients in the HBOT group. All patients received prophylactic phenytoin. |
| ***Studies of other brain injury*** | | | |
| Jianhua 1995[106] China (Poor) | HBOT group: 18/47 (38%) curative, 25/47 (53%) effective, 3/47 (6%) ineffective (1 missing?).<br>Control group: 8/45 (18%) curative, 20/45 (44%) effective, 17/45 (38%) ineffective.<br>HBOT vs control: % curative *p* < 0.05, % effective p > 0.05, % ineffective *p* < 0.001. | Not reported. | |

HBOT=hyperbaric oxygen therapy; GCS=Glasgow Coma Scale; GOS=Glasgow Outcomes Scale; atm= atmospheres; NS= non-significant; ICP=intracranial pressure; CT=computerized tomography; EEG=electroencephalogram

## Evidence Table 2. Brain injury observational study data

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions |
|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | |
| Artru 1976[94] France (Fair) | Patients in coma from head injuries with brain stem contusions. 4 of 6 in "deep coma," mean coma duration 2.3 months. | 2.5 atm x 60 minutes (10-minute compression & 20-minute decompression phase before & after), duration, number of treatments not reported. One patient compressed at 2.2 atm due to a bad pulmonary condition. One used respirator, others breathed spontaneously in chamber. (Type of chamber not specified) | None. |
| Hayakawa 1971[95] Japan (Fair) | Patients with acute cerebral damage; 9 with closed head injury in acute post-traumatic period, 4 had craniotomy for brain tumor and were in the immediate postoperative state. All had severe neurological disorders and were comatose. Six were breathing spontaneously, 7 had intermittent positive pressure ventilation. | 2.0 atm x 60 minutes. (Multiplace chamber; oxygen administered with non-rebreathing face mask or endotracheal tube) | None reported. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | | |
| Artru 1976[94] France (Poor) | Before-after | 6 | Cerebral blood flow, other lab tests, change in clinical status. | Tests given immediately following treatment (within hours). |
| Hayakawa 1971[95] Japan (Fair) | Time-series | 13 | Cerebrospinal fluid pressure measured continuously during HBOT with a water manometer connected to a catheter inserted into the lateral ventricle of the cerebrum via a burr hole in the frontal lobe. | Measured before, during and after (up to 100 minutes). |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | |
| Artru 1976[94] France (Poor) | 2 patients (33%) found neurologically improved at exit from the chamber; the first recovered sufficient consciousness to answer simple questions, the second was able to keep his eyes open and showed an improved motor reactivity on one side. However, both patients sunk to pre HBOT status by second cerebral blood flow test (mean time to test = 2hr 20min). No other patients recovered consciousness. 3 of 6 (50%) dead at conclusion of study. | One patient developed a status epilepticus on one side that took 12 hours to control. | |
| Hayakawa 1971[95] Japan (Fair) | 3 patterns of responses noted: Response 1 (69%): ICP fell with HBOT after initial fluctuation eased by the beginning of compression, reverted rapidly with decompression at end of HBOT. After cessation of HBOT, ICP commonly showed temporary rebound & considerably exceeded pretreatment level. Even during HBOT, ICP which had initially fallen by HBOT was liable to increase gradually with passage of time, & upward tendency during HBOT more striking when HBOT continued beyond about 30 minutes. Response 2 (15% pts): ICP showed little rebound & the ICP after HBOT significantly lower than the pretreatment level. Response 3 (15%): ICP showed little response to HBOT, & maintained a consistently low or high level during and after HBOT. | | |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon dioxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions |
|---|---|---|---|
| Mogami 1969[96] Japan (Poor) | Patients with acute cerebral damage (evidence of severe brain damage from any cause). | 2.0 atm x 60 minutes once or twice daily, total number of treatments not stated. 6 treatments given at 3.0 atm x 30 minutes. (Multiplace with non-rebreathing face mask or tracheal tube) | None. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| Mogami 1969[96] Japan (Poor) | Before-after | 66<br>51 with TBI | Not clearly stated in methods. Neurologic signs and symptoms, EEG, cerebrospinal fluid pressure, and cerebrospinal fluid lactate and pyruvate levels reported for some patients. | Not clear when or if baseline measurements taken, followup appears to be during and immediately after treatments. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Mogami 1969[96] Japan (Poor) | Of 51 patients with TBI:<br>Clinical improvement (categories not defined) during HBOT treatment:<br>33% "great" improvement, 16% "some," 51% "none."<br>Most of the favorable responses were temporary and regression to pretreatment level occurred immediately after decompression. Authors note that effects more prominent in milder injury.<br>3 patients became convalescent with the definite help of HBOT (diagnosis not reported), especially one (TBI patient) who was discharged with only mild residual neurological deficit.<br>4 (diagnosis not reported) showed clinical improvement during HBOT but became much worse afterward, 1 died. One TBI patient's seizures became worse during HBOT.<br>ICP: Reported that ICP generally fell with HBOT, reverting rapidly with decompression. A rebound phenomenon was noted, with pressures exceeding pretreatment levels. Two cases showed no response, and two showed no rebound. No further details given. | In one patient, seizures caused by head injury slightly increased during HBOT. | |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon dioxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions |
|---|---|---|---|
| Ren 2001[99] China (Poor) | Patients with severe (GCS score < 8) closed head injury. Admitted within 24 hours of injury. Patients with organ injuries or open head injury excluded, patients who died excluded from analysis. | 2.5 atm x 40-60 minutes once daily with 10 minute break x 10 treatments per course x 3-4 courses. After each course a 4-day intermission followed. Begun on third day after stabilization. | Both groups received routine treatment (dehydration, steroid and antibiotics). |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| Ren 2001[99] China (Poor) | Cohort | 35 HBOT<br>20 control | GCS and GOS | Baseline measure (GCS) on third day after injury (before HBOT), second week (after 1 course of HBOT), and second month (after 3 courses of HBOT). Prognosis (GOS) at 6 months. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Ren 2001[99] China (Poor) | Mean GCS score,<br>HBOT group: before treatment 5.1, after 1 course 10.1 ($p$ < 0.01); after 3 courses 14.6 ($p$ < 0.01 compared to initial injury)<br>Control: before treatment 5.3, after 1 course 8.1, after 3 courses 9.5. (NS)<br>After 3 courses of treatment, GCS score vs control group score higher ($p$ < 0.01)<br>Good recovery or mild disability at 6 months: 29/35 (HBOT) 6/20 (control), $p$ < 0.001<br>GOS: good recovery or mild disability: 29/35 (83.7%) HBOT, 6/20 (30%) control ($p$ < 0.01) | Not reported. | Some differences. More women in HBOT group than control (29 vs 15%), CT findings (more subdural hematoma in HBOT group); small difference in baseline GCS (5.3 vs 5.1). |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon dioxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions |
|---|---|---|---|
| Rockswald 2001[97] Minnesota (Fair) | Patients treated for traumatic, severe closed-head injuries at one Level I Trauma Center; mean age 36 +/- 3 years (range 8-84). 27 male, 10 female. Severe brain injury defined as GCS score 8 or less. Mean GCS score at study entry was 5.8 +/- 0.3. Inclusion criteria CT scan score greater than II according to Traumatic Coma Data Bank. Exclusion criteria were condition not compatible with HBOT, such as unstable pulmonary status or pregnant, unstable fracture that prevented placement in chamber, under age 4 years, and patients placed in a barbiturate-induced coma during initial case management. | Compression at a rate of 1 psi per minute x 15 minutes, 1.5 atm x 60 minutes, then decompressed at the same rate. First HBOT treatment performed as soon as entry criteria were met and the patient was deemed clinically stable; mean time from injury to initial treatment was 23 (+/- 2) hours (range 9-49 hours). Second treatment was given the next morning, with a minimum of 8 hours separating the 2 sessions. Subsequent treatments were given 24 hours apart for up to 5 more days (maximum of 7 treatments per patient) or until the patient could consistently obey simple commands or was deemed brain dead. Treatments were stopped if the patient became medically unstable due to sepsis or uncontrolled blood pressure, or if the addition of a pentobarbital-induced coma to the treatment strategy was necessary for control of ICP. A total of 167 HBOT treatments were administered, for an average of 5 treatments per patient. (32 patients used monoplace chamber, 5 multiplace) | Intensive neurosurgical care paralleled Guidelines of the Brain Trauma Foundation, including stabilization with early intubation while patient in ED, surgical evacuation of significant hematomas, continuous monitoring of ICP, treatment of ICPs greater than 15 mm Hg. All received prophylactic phenytoin sodium. All received ventilation therapy throughout entire study period. Bilateral myringotomies performed on all. An ICP over 15 mm Hg was treated, sequentially including hyperventilation, CSF drainage, administration of mannitol, and finally barbiturate therapy. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| Rockswald 2001[97] Minnesota (Fair) | Time-series | 37 | ICP monitored using tunneled ventriculostomy. | ICP values recorded hourly in the neurological ICU and every 15 minutes during HBOT treatments. One hour before treatment, during treatment, 1 hour after depressurization to 1 atm, and 6 hours after the session in the chamber. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Rockswald 2001[97] Minnesota (Fair) | Low pretreatment ICP values (<15 mm Hg) were increased 1 hour and 6 hours after the session ($p < 0.001$). High pretreatment ICP values (> 15 mm Hg) were decreased 1 hour and 6 hours after HBOT sessions ($p = 0.006$). ICP values in both categories rose throughout the session ( $p < 0.001$), the only difference being a trend for high pretreatment ICP values to drop during the first 15 minutes of the treatment session. ICP rose linearly during the treatment session in all patients. | Not reported. | |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon dioxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions |
|---|---|---|---|
| Sukoff 1982[98] California (Poor) | Patients with traumatic encephalopathy (cerebral contusion). Sustained depressed level of consciousness, unable to obey commands, decerebrate or decorticate, brain stem dysfunction, and pupillary abnormalities. | 2.0 atm x 45 minutes every 8 hours x 48 hours if ICP was under 15 mm Hg. If over 15 mm Hg after mannitol, every 4 hours for 2-4 days depending on response. (Monoplace chamber.) | Standard therapeutic measures were the same in both groups, except that no barbiturates given to elevated ICP patients under HBOT protocol. |
| ***Studies of other brain injury*** | | | |
| Chuba 1997[107] Michigan (Poor) | Patients with radiation-induced necrosis of the central nervous system. New or increasing neurologic deficits after radiotherapy. Ages 4-23 years. | 2.0-2.4 atm x 90 minutes-2 hours x minimum of 20 treatments. (Multiplace chamber) | None. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| Sukoff 1982[98] California (Poor) | Before-after | 50 (10 with ICP data reported) | ICP, neurologic symptoms. | Pre- and post-treatment. |
| ***Studies of other brain injury*** | | | | |
| Chuba 1997[107] Michigan (Poor) | Before-after | 10 | Symptoms and imaging findings attributed to radiation-induced necrosis were scored as improved, worsened or stabilized after HBOT. | Timing of baseline and followup evaluation not stated. |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Sukoff 1982[98] California (Poor) | In elevated ICP group (10 patients), all but one patient demonstrated some degree of improvement during initial treatment session, mostly minor. Improvement in chamber was manifested by increased awareness and motor activity. The ability to obey commands was enhanced, and verbalization was more prompt and more appropriate in those patients whose pretreatment status had included some verbal abilities.<br>In the other 40 patients, 22/40 (55%) improved during HBOT treatment. Patients less severely compromised neurologically showed better and more sustained improvement. Details not given, only EEG and CT scan results.<br><br>10 patients had ICP monitoring continuously. ICP decreased during HBOT in all cases. Reduction was 4-21 mm Hg below the pretreatment level. Difference between ICP before and during HBOT $p < 0.001$. Lower pressures were sustained for 2 to 4 hours after HBOT in "most" cases (number not specified). In some instances in 2 patients, at 1 or 2 hours after treatment, ICP was near or slightly higher than pre-HBOT exposure. | In elevated ICP group, one patient died of systemic problems 6 days after the last HBOT exposure. Two patients had seizures. No pulmonary complications attributed to HBOT.<br>In non-elevated ICP group four myringotomies were required for barotrauma, increased restlessness in some patients. Five patients died of systemic problems or progressive cerebral insufficiency. No pulmonary or central nervous system complications attributed to HBOT. | Patients requiring continuous vasopressors for hypotension due to systemic trauma and those with dilated and fixed pupils were excluded. No steroids were given. |
| ***Studies of other brain injury*** | | | |
| Chuba 1997[107] Michigan (Poor) | Following treatment, of 10 patients, symptoms of 40% improved, 20% improved initially, 10% stabilized, 20% stabilized initially, 10% resolved. At followup ranging from 3 to 36 months, 40% died, 10% alive with tumor, 20% alive (not specified if still with disease), 30% alive with no evidence of disease. | One patient developed ear pain and required myringotomy tubes. Treatments discontinued in one patient due to sinusitis. | All patients had failed steroid therapy prior to HBOT. In two of the patients the diagnosis was made on radiological basis, all others by biopsy. |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon dioxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions |
|---|---|---|---|
| Imai 1974[108] Japan (Poor) | Patients with CO intoxication with residual symptoms (N=2). Report also includes patients with chronic alcoholism, presenile dementia, chronic atherosclerosis (results not reported here), and cerebral thrombosis (results reported in stroke table) | 1.3 atm x 60 minutes daily x 5 sessions. (Monoplace chamber) | None. |
| Mathieu 1987[109] France (Poor) | Patients admitted to one emergency unit after unsuccessful hanging from 1971-1981. Age range 10-83. 19 were conscious or slightly "obnubilated," 151 had altered consciousness level. On GCS, 54 grade 1, 26 grade 2, 30 grade 3, 31 grade 4. Brain death was pronounced in 10. Patients admitted to department for unsuccessful hanging, only patients with impaired consciousness levels were selected for HBOT. | 2.5 atm x 90 minutes repeated until the conscious level returned to normal. When several courses were needed, they were separated by 6-hour intervals. 278 courses provided to 136 pts. (Monoplace chamber; pure oxygen chamber used until 1978, then chamber in which oxygen administered by facial mask or assisted ventilation) | Steroids or beta-1-24-tetracosactide was used in every comatose patient until recovery of consciousness or the 3rd day. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|
| Imai 1974[108] Japan (Poor) | Before-after | 32 (report states 30, but numbers total 32); 2 with sequelae from CO poisoning. | Memory testing, that included Bender-Gestalt test as one item of 9, tests given after 1 or 2 courses of treatment | Unclear if and when baseline conducted. Followup conducted after one or two sessions. |
| Mathieu 1987[109] France (Poor) | Before-after | 136 | Recovery, with or without neurological sequelae, mortality. | Not clear. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon monoxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 2. Brain injury observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Imai 1974[108] Japan (Poor) | 5% to 10% improvement in overall score (individual scores not given), with 10% to 15% improvement on visual reproduction (based on Bender-Gestalt test) and story recall (not described) elements. | Not reported. | Results reported only ranges of percentage improvement. Unclear how subjects chosen. |
| Mathieu 1987[109] France (Poor) | 108/136 (79%) recovered without residual effects, 8/136 (6%) recovered with neurological sequelae (chronic coma 3 cases, locked-in syndrome 2 cases, extrapyramidal rigidity 1 case, hemiplegia 1 case, hemiasomatognosia 1 case), 20/136 (15%) treatment failure. | After admission, complications occurred in 10 patients and were cause of death even when neurologic state improved: pulmonary edema 5 cases, pulmonary infection 4 cases, cardiac arrest 1 case. Relationship with HBOT in only 3 of these cases: 2 pulmonary edema occurred during the course of HBOT, and the cardiac arrest patient could not be resuscitated in time because of the monoplace chamber. | |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; GCS=Glasgow Coma Scale; CO=carbon dioxide; GOS= Glasgow Outcomes Scale; ED=emergency department; CSF= cerebrospinal fluid; EEG= electroencephalogram; TBI=traumatic brain injury; psi=pounds per square inch

## Evidence Table 3. Cerebral palsy controlled trial data

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Control | Randomized? | Baseline differences between groups? |
|---|---|---|---|---|---|
| Collet 2001[119] Hardy 2002[120] Canada (Fair) | Children with CP with history of hypoxia in perinatal period, age 3-12 years, motor development age of 6 months to 4 years, and psychological development age 24 months or more. | 100% oxygen at 1.75 atm x 60 minutes x 40 sessions. Sessions 5 days/week x 8 weeks.<br><br>(Monoplace or multiplace chamber, depending on facility used) | Room air at 1.3 atm x 60 minutes x 40 sessions. Sessions 5 days/week x 8 weeks. | Yes | Some differences in presumed cause and type of CP. |
| Packard 2000[118] New York (Poor) | Children age 15 months to 5 years, with CP secondary to prenatal insults, premature birth, birth asphyxia, and post-natal hemorrhage. Criteria for enrollment were age between 1 and 5 years, moderate to severe CP, no evidence of brain malformation, developmental delay of at least 33% in one area, and no active seizures for the previous 6 months. | 1.5 atm x 60 minutes twice daily x 40. Five days per week for 4 weeks.<br>(Chamber type not given) | Delayed HBOT treatment. | Yes | Not reported beyond subjects "matched roughly to age and severity." |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; NS=non-significant; PEDI= Pediatric Evaluation of Disabilities Inventory; GMFM=Gross Motor Function Measure

## Evidence Table 3. Cerebral palsy controlled trial data (continued)

| Author, year, location (Quality) | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|
| Collet 2001[119] Hardy 2002[120] Canada (Fair) | 111 (57 HBOT, 54 control) for motor function based tests, 75 for neuropsychiatric tests | Primary outcome measure: Gross motor function as assessed by the GMFM. Other outcomes measured using a variety of tests/protocols, including neuropsychological testing based on 5 measures. | Assessed at baseline, after 20 and 40 treatments, and 3 months later. |
| Packard 2000[118] New York (Poor) | 26 (12 immediate treatment group, 14 delayed treatment group) | Weekly parent diaries, neuro-developmental assessment, Bayley II (cognitive assessment) Preschool Language Scale (language assessment), Peabody Motor Scales (assessment of gross and fine motor skills), PEDI (Parental report of specific skill in mobility, self-care, and social interactions). | Assessments at T1 (at enrollment), T2 (after the immediate group received treatment), T3 (prior to the delayed group's HBOT, 5 months after enrollment), and T4 (after the delayed group's treatments). |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; NS=non-significant; PEDI= Pediatric Evaluation of Disabilities Inventory; GMFM=Gross Motor Function Measure

## Evidence Table 3. Cerebral palsy controlled trial data (continued)

| Author, year, location (Quality) | Results |
|---|---|
| Collet 2001[119] Hardy 2002[120] Canada (Fair) | Change in Global GMFM<br>Post-intervention (after 40 treatments):<br>HBOT: 2.9 (95% CI, 1.9, 3.9)<br>Control: 3.0 (95% CI, 2.1, 3.9)<br>*p* = 0.54<br>At 3 months:<br>HBOT: 3.4 (95% CI, 2.2, 4.5)<br>Control: 3.1 (95% CI, 2.2, 4.1)<br>*p* = 0.97<br>Secondary outcome measures:<br>NS for between group comparisons for all tests, including neuropsychological tests. |
| Packard 2000[118] New York (Poor) | Parental diaries:<br>83% of parents noted a marked improvement in mobility, 43% saw a marked increase in attention, and 39% reported a marked increase in language skills. There was some improvement in mobility in 21 of 23 children (91%), attention in 18/23 (78%), language in 20/23 (87%), and play in 12/23 (52%). One family saw no improvement and 6 saw minimal improvement (30%). Five families (22%) reported major gains in skills and 11 (48%) reported modest gains.<br>Improvement in vision:<br>4/9 (44%) children with cortical visual impairment had improvement in vision noted by families, vision therapists, and ophthalmologists.<br>PEDI Results:<br>Improved scores on mobility sub-domains of PEDI for time period T2 minus T1 in favor of immediately treated group (p<0.05), trend favoring recently treated delayed group for time period T4 minus T3 (*p* <0.058).<br>For social function sub-domain, trend favoring more recent treated group (p not given).<br>Blinded Assessments:<br>No statistical difference in the change scores on any of the blinded assessments (change in Peabody scores for T2 minus T1 and T4 minus T3; change in Bayley II and PLS scores for T3 minus T1),<br>(*p* values not given).<br><br>In followup interviews with parents after 6 months, it was found that changes in spasticity were most likely to diminish over time, but the improvement in attention, language, and play remained. |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; NS=non-significant; PEDI= Pediatric Evaluation of Disabilities Inventory; GMFM=Gross Motor Function Measure

## Evidence Table 3. Cerebral palsy controlled trial data (continued)

| Author, Year, Location (Quality) | Adverse effects | Comments |
|---|---|---|
| Collet 2001[115] Hardy 2002[116] Canada (Fair) | One withdrawal for side effects, not stated which group. 27 patients in HBOT group and 12 in control group had ear problems (p = 0.004) | Masking of parents and assessors, statistical analysis described, loss to followup reported. Patients with physical disability preventing them from using a computer with at least one hand were excluded from neuropsychologic testing. |
| Packard 2000[114] New York (Poor) | 3/26 (12%) patients developed seizures and could not complete treatment. Nine children and 7 parents required ventilation tube placement or myringotomies for barotrauma to the middle ear. | 11/12 (92%) in immediate group and 12/14 (86%)in delayed group completed 40 sessions. |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; NS=non-significant; PEDI= Pediatric Evaluation of Disabilities Inventory; GMFM=Gross Motor Function Measure

## Evidence Table 4. Cerebral palsy observational study data

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Chavdarov 2002[121] Bulgaria (Fair) | Children with CP selected from a population of children treated and followed at one residential treatment center. 15 females and 35 males, mean age 5 years 9 months (range 1 year 7 months to 19 years); No history of seizures, age over 1 year 6 months, not having complaints about lungs, heart, ears, or naso-pharynx; parental consent. | 1.5 to 1.7 atm x 40 to 50 minutes (including 10 minutes compression, 20 to 30 minutes iso-compression, and 10 minutes decompression) once daily x 20 consecutive days. (Multiplace, oxygen administered through a hood) | Vitamin C | Time-series | 50 |
| Machado 1989[122] Brazil (Poor) | Children with CP age under 1 year to 15 years. | 1.5 atm x 1 or 2 maximum hours per day x 20 sessions. (Monoplace) | Not reported | Time-series | 230 |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; GMFM=Gross Motor Function Measure; EEG=electroencephologram; CT=computerized tomography

## Evidence Table 4. Cerebral palsy observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Chavdarov 2002[121] Bulgaria (Fair) | Motor developmental level classified by Gross Motor Function Classification System at baseline, motor abilities measured by Holt's Assessment of Motor Abilities, mental abilities by Munich's Functional Developmental Diagnostic, Wechsler's test for children, Raven's test for children, Frostig's test, Goppinger's test; speech abilities assessed by Munich's Functional Developmental Diagnostic, Nancie Finnie's Questionnaire, Wechsler's test for children. Assessments by physiotherapists, psychologists, speech therapists. | All measurements repeated on two consecutive days before and after the period of HBOT by the same specialist. |
| Machado 1989[122] Brazil (Poor) | Neurological exam, including a spasticity rating of 0 to 100. Some patients also had EEG and/or CT scans. | Baseline, immediately after, and "6 or more months after" HBOT |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; GMFM=Gross Motor Function Measure; EEG=electroencephologram; CT=computerized tomography

## Evidence Table 4. Cerebral palsy observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Chavdarov 2002[121] Bulgaria (Fair) | Change after HBOT:<br>Motor abilities: moderate improvement 6/46 (13%), mild improvement 13/46 (28%), no improvement 27/46 (59%).<br>Mental abilities: 2/34 (6%) moderate improvement, 10/34 (29%) mild improvement, 22/34 (65%) no improvement.<br>Speech abilities: moderate improvement 3/41 (7%), mild improvement 15/41 (37%), no improvement 23/41 (56%). | 4/50 (8%) stopped treatments because of unwanted effects, including seizures, oral automatic movements, hyperesthesia of the face, extreme increasing pulse rate. | |
| Machado 1989[122] Brazil (Poor) | Immediately after HBOT: 218/230 (95%) patients had clear reduction of spasticity (nearly 50% less). Frequently, clonus or Babinski sign would disappear, with better plantar support and abolition of leg "scissoring."<br>12/230 (5%) remained unchanged.<br>In 82 patients followed for 6 or more months: 76% had persisting reduction of spasticity & better motor control. Parents reported other types of improvement, such as better balance, more attentive, more "intelligent" with reduced frequency of convulsions & episodes of bronchitis.<br>24% were apparently unchanged. | One parent found daughter to be worse, with convulsions some time after the course of HBOT. | This is acknowledged to be only a reporting of this facility's experiences, is not intended as a scientific study. |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; GMFM=Gross Motor Function Measure; EEG=electroencephologram; CT=computerized tomography

## Evidence Table 4. Cerebral palsy observational study data

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Montgomery 1999[123] Canada (Fair) | Children with CP and a functional diagnosis of spastic diplegia. Age 3 to 8 years (mean 5.6 years). | 95% oxygen at 1.75 atm x 60 minutes x 20 sessions. 10 of the patients received 1 treatment daily x 5 days per week x 4 weeks in a monoplace chamber. The other 15 received 2 treatments daily x 5 days per week x 2 weeks in a multiplace chamber. (Either monoplace or multiplace) | None | Before-after | 25 |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; GMFM=Gross Motor Function Measure; EEG=electroencephologram; CT=computerized tomography

## Evidence Table 4. Cerebral palsy observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Montgomery 1999[123] Canada (Fair) | GMFM; fine motor function by Jebsen's test, and spasticity level by the modified Ashworth scale. Videotapes of motor function also assessed by physical therapists. Oral questionnaires on physical functioning administered by physical therapists. | Pre- and post-treatment evaluations separated by a mean of 37.2 (+/- 8) days. |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; GMFM=Gross Motor Function Measure; EEG=electroencephologram; CT=computerized tomography

## Evidence Table 4. Cerebral palsy observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Montgomery 1999[123] Canada (Fair) | On GMFM, significant improvements ($p < 0.05$) observed for 3 of 5 dimensions: sitting, standing, walking/running/jumping. Not on lying/rolling or crawling/kneeling. Average improvement in total GMFM score was 5.3%.<br>Functional evaluation of hand: Significant improvement on 3 of 6 tests: turning cards, moving large cans, and moving weighted cans. Not on picking up small objects & placing in a container, stacking checkers, or simulated eating.<br>Spasticity: Physician determined significant reduction in spasticity in hip abductors, hamstrings, ankle plantar flexors. Physical therapist noted improvement only in left quadriceps femoris.<br>Video analysis of gross motor function: better movement post-test in 16/24 (67%) children, better pre-test in 7/24 (29%), and equal for 1/24 (4%).<br>On parent questionnaire, significant improvement occurred for 4 of 9 activities: walking, high kneeling, sitting on the floor, and sitting on a bench. The proportion of patients whose scores improved for each of these items were 38%, 33%, 50%, and 42%, respectively. Scores were not improved for crawling, undressing ($p = 0.07$), eating, personal hygiene, or communication. | Pressure equalization tubes inserted in 13 children, all using multiplace chamber, none using monoplace chamber. | Pressure equalization tubes were given to 13 children in the multiplace unit to aid in compression discomfort. Subjects selected randomly from a total pool of 60 potential then randomly assigned to the HBOT protocol administered. |



HBOT=hyperbaric oxygen therapy; CP=cerebral palsy; atm=atmospheres; GMFM=Gross Motor Function Measure; EEG=electroencephologram; CT=computerized tomography

## Evidence Table 5. Stroke controlled trial data

| Author, year, location (Quality) | Population | HBOT Protocol (Type of chamber) | Control |
|---|---|---|---|
| Anderson 1991[127] Minnesota (Fair) | Patients with ischemic cerebral infarction. | 100% oxygen at 1.5 atm x 60 minutes every 8 hours x 15 treatments. Standard ICU plus physical and occupational therapy. Vitamin E 400 units given with each HBOT session. (Monoplace) | Room air at 1.5 atm x 60 minutes every 8 hours x 15 treatments. Standard ICU plus physical and occupational therapy. |
| Marroni 1987[129] Italy (Poor) | Stabilized stroke patients no longer undergoing any form of therapy or rehabilitation, 69% male, mean age 59.7 (range 24-78), who had a stroke from 2 to 172 months earlier (average 29.2 months). | Group C1: HBOT at 2.0 atm x 60 minutes x 30 sessions<br>Group C2: Same as C1 at 1.5 ata<br>Group D1: HBOT + Rehab: 30 in-water, 40-minute morning rehab sessions (water temperature 30 degrees celsius) and HBOT 2.0 atm x 60minutes x 30 afternoon sessions.<br>Group D2: Same as D1 at 1.5 ata<br>Group E1: HBOT Rehab: 30 simultaneous, 60-minute HBOT and 40-minute in-water rehab sessions (water temp 30 degrees celsius) in specially-built hyperbaric pool at 2.0 ata.<br>Group E2: Same as E1 at 1.5 ata.<br>(BIBS mask overboard dump system)? | Group A: No treatment,<br>Group B: 30 in-water physical therapy sessions x 40 minutes in 30 degree celsius water. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Randomized? | Baseline differences between groups | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Anderson 1991[127] Minnesota (Fair) | Yes | Small difference in age, other factors similar, including baseline neurologic scores. | 20 HBOT<br>19 control | Graded neurological exam (0 to 100), volume of hypodensity on CT scan. | Neurological exam administered at entry, 5 days, 6 weeks, 4 months, and 1 year. Hypodensity measured at 4 months. |
| Marroni 1987[129] Italy (Poor) | No | Not reported. | 80 total:<br>11 A<br>7 B<br>15 C1<br>10 C2<br>9 D1<br>7 D2<br>12 E1<br>9 E2 | All patients evaluated using Kurtzke scale before entering protocol, then at days 10, 20, and 30 of treatment and 1 and 3 months after treatment . At the same time, all pts scored according to an original neuromotor disability evaluation scale (given in paper). | Patients evaluated before entering protocol, then at days 10, 20, and 30 of treatment and 1 and 3 months after treatment. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Anderson 1991[127] Minnesota (Fair) | Average graded neurological exam scores<br>Baseline: 44.6 (control), 45.5 (HBOT):<br>Day 5: 38.5 (control), 43.8 (HBOT) $p = 0.54$<br>Week 6: 28.3 (control), 38.5 (HBOT) $p = 0.25$<br>Month 4: 25.6 (control), 34.5 (HBOT) $p = 0.33$<br>Year 1: 25.8 (control), 31.4 (HBOT) $p = 0.53$ | 2 complications (group not clear): 1 patient with a history of psychiatric illness became acutely psychotic in the chamber, 1 developed atelectasis the authors believe was exacerbated by sedation and suspension of pulmonary toilet during treatment. No seizures.<br>8/39 (21%) patients refused to continue treatments (not specified from which groups). | Study suspended after enrollment of 39 patients when a safety monitoring committee detected an outcome trend favoring sham treatment. |
| Marroni 1987[129] Italy (Poor) | Evaluation of general disability according to the Kurtzke functional scale showed improvement between 1 and 1.8 degrees in HBOT groups; non-HBOT groups did not show notable changes. Using an unvalidated scale developed by the authors, all dry HBOT groups showed greater improvement in their motor ability, but no clear-cut difference could be observed among the 4 groups that scored improvements of from 3.1 to 3.8 degrees. HBOT 1.5 atm rehab group reached 8.1 degrees 1 month after treatment, leveling off to 7.7 at 3 months, and the 2.0 atm HBOT rehab group showed an 11.6 degree improvement still present 3 months after treatment. The scale ranged from 17 (best) to 111 (worst) points. No statistical analysis, data presented graphically as means only. | Not reported. | |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Population | HBOT Protocol (Type of chamber) | Control |
|---|---|---|---|
| Nighoghossian 1995[126] France (Poor) | Patients with ischemic stroke in middle cerebral artery confirmed by CT and seen within 24 hours of onset. | 100% oxygen at 1.5 atm x 40 minutes daily x 10 treatments. (Monoplace) | Room air at 1.5 atm x 40 minutes daily x 10 treatments. |
| Rusyniak 2003[131] Indiana (Fair) | Patients presenting to Emergency Department within 24 hours of onset of symptoms and measurable deficit by NIHSS and without evidence of hemorrhage by CT scan. | 100% oxygen at 2.5 atm x 1 hour x 1 session (Monoplace) | Control: 100% oxygen at 1.14 atm x 1 hour x 1 session |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Randomized? | Baseline differences between groups | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Nighoghossian 1995[126] France (Poor) | Yes | Not clear, Orgogozo scale lower in control group at baseline (not statistically significant). | 17 HBOT<br>17 control | Three scales: Orgogozo scale, Rankin disability scale, and Trouilla scale. | Only Orgogozo scale administered at baseline, all three administered at 6 months and 1 year. |
| Rusyniak 2003[131] Indiana (Fair) | Yes | Some differences in age gender and race (HBOT group older, fewer women, more Black patients) | 17 HBOT<br>16 control | Primary outcome = Proportion with "good" outcome on NIHSS at 24 hours and 90 days (score of 0 or improvement of >4 points) and on Barthel Index (score 95 or 100), Modified Rankin score (score </= 1), and GOS (score = 5) at 90 days<br>Secondary outcomes = mortality and adverse events | Only NIHSS at baseline. Follow up at 24 hours and 90 days |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Nighoghossian 1995[126] France (Poor) | Difference in mean score (HBOT-Control) on Orgogozo scale:<br>6 months: 18.2 (-3.4, 39.9) (NS)<br>1 year: 27.9 (6.0, 50.0) ($p$ = 0.02)<br>*On Trouillas scale:*<br>6 months: -1.5 (-3.3, 0.3) (NS)<br>1 year: -2.2 (-4.2, -0.2) ($p$ = 0.13)<br>*On Rankin scale:*<br>6 months: -0.6 (-1.5, 0.2) (NS)<br>1 year: -0.6 (1.5, 0.2) (NS)<br><br>Pretherapeutic and posttherapeutic differences (HBOT-Control)<br>*On Orgogozo scale:*<br>Difference (6 months -baseline): 7.1 (-14.6, 28) $p$ = 0.51<br>Difference (1 year - baseline): 16.8 (-6.9, 40.4) $p$ = 0.16<br>*On Trouillas scale:*<br>Difference (1 year - 6 months): -0.6 (-1.6, 0.4) $p$ = 0.50<br>*On Rankin scale:*<br>Difference (1 year - 6 months): 0.1 (-0.3, 0.5) $p$ = 0.78 | Treatment discontinued in 7 patients (21%): 4 due to worsening of neurological status in first week (3 died), 3 patients had myocardial infarction, worsening of neurological condition related to ischemic injury, and claustrophobia. | |
| Rusyniak 2003[131] Indiana (Fair) | Proportion with good outcome on NIHSS at<br>24 hours: HBOT 18%, control 31%, p=0.44<br>90 days: HBOT 29%, control 50% p=0.30 (ITT)<br>90 days: HBOT 31%, control 80% p=0.04 (PP)<br><br>Proportion with good outcome at 90 days on:<br>Barthel Index: HBOT 47%, control 56%, p=0.73 (ITT)<br>HBOT 50%, control 82%, p=0.12 (PP)<br>Modified Rankin score: HBOT 29%, control 56%, p=0.17 (ITT)<br>HBOT 31%, control 82% p=0.02 (PP)<br>GOS: HBOT 35%, control 63% p = 0.17 (ITT)<br>HBOT 38%, control 91% p = 0.01 (PP) | HBOT: 2 patients (ear pain, claustrophobia)<br>Control: 3 patients (claustrophobia) (p=0.44)<br>Deaths: HBOT: 1, Control 2 (p=0.6) | Planned as a pilot study, no power calculations. |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Population | HBOT Protocol (Type of chamber) | Control |
|---|---|---|---|
| Sarno, JE 1972[128]<br>Sarno, MT 1972[130]<br>New York<br>(Fair) | Patients with vascular stroke at least 3 months post-stroke. Mean age 60.5 years, range 42-82. In MT Sarno, subset of 16 patients with left-brain damage, right hemiplegic patients. Mean age 62, range 44-82. | 100% oxygen at 2.0 atm x 1.5 hours x 1 session. (Multiplace. In early phase of the study, plastic hood sealed with tape was used, but patients complained of confinement and claustrophobia. Changed to mask) | 10.5% oxygen at 2.0 atm x 1.5 hours x 1 session. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Randomized? | Baseline differences between groups | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Sarno, JE 1972[128] Sarno, MT 1972[130] New York (Fair) | Yes (randomized crossover) | Not reported. | 32 (all received both HBOT and control) (subset of 16 reported in MT Sarno) | Cognitive-perceptual testing (Token Test and Functional Communication Profile) and communication testing (those with right brain damage were only given the cognitive-perceptual tests). | Communication baseline done 24 hours prior to exposure, immediately after HBOT treatment. Baseline cognitive test given in the chamber with mask in place. The followup done in chamber after exposed to 2.0 atm for 30 minutes. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 5. Stroke controlled trial data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Sarno, JE 1972[128]<br>Sarno, MT 1972[130]<br>New York<br>(Fair) | No significant effect on any measure. | Not reported. | |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; CT=computerized tomography; ICU=intensive care unit; NS=non-significant; NIHSS=National Institutes of Health Stroke Scale; GOS=Glascow Outcomes Scale; ITT=intention-to-treat-analysis; PP=per-protocol analysis

## Evidence Table 6. Stroke observational study data

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Hart 1973[149] California (Poor) | Patients referred with middle cerebral artery ischemia. Neurologic state unchanging for at least 3 weeks and at least 4 weeks from onset of ischemic attack. Excluded if untreated malignancy, severe emphysema, or uncontrollable claustrophobia. Had to refrain from nicotine use. | 2.5 atm x 90 minutes daily x 15 days. Allowed to rest for 30 days and if measurable improvement had occurred, a second series of 15 treatments administered. (Monoplace) | Methyldopa, 250 mg tid, acetazolamide 500 mg 1 hour prior to treatment, or cyclandelate 200 mg bid, alpha-tocopheroll 25 mg qid, anticoagulation (coumadin preferred). Idiazepam 10 mg im tid if apprehensive; physical therapy, gait training, and speech therapy. | Before-after | 40 |
| Heyman 1966[133] North Carolina (Poor) | Patients with neurologic deficits caused by various forms of cerebral vascular disease. Clinical manifestations of cerebral ischemia were sudden in onset, clearly defined, and usually consisted of hemiplegia, hemisensory loss, aphasia, and coma. One hour to 30 days since onset of symptoms. | 2.0 to 3.0 ata. Duration and extent of compression selected in each patient to minimize the risk of oxygen toxicity. In initial studies patients had 3.04 atm for less than 1 hour. In later treatments, used 2.5 atm to allow prolonged exposure (duration not specified). (Chamber type not reported, used mask or head tent) | Myringotomies performed prior to compression. | Time-series | 22 |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Hart 1973[149] California (Poor) | Improved neurological exam (tests not specified), death. | Complete neurological exam and EEG prior to onset of therapy, not clear when followup exams done. |
| Heyman 1966[133] North Carolina (Poor) | Clinical and neurologic changes (observations). | Not clear how long followup was, clinical and neurologic changes monitored throughout HBOT procedure and at frequent intervals thereafter. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Hart 1973[149] California (Poor) | 7/40 (17.5%) died, 33 (82.5%) improved; 11/15 (73%) aphasic improved. | One patient became worse during therapy (found at autopsy to have a cerebral metastasis). | |
| Heyman 1966[133] North Carolina (Poor) | Of 15 patients whose symptoms began within the preceding several hours, 4 (27%) improved dramatically during HBOT, with complete or almost complete restoration of neurologic and mental function, immediate reversal of paralysis with return of strength and ability to perform fine controlled movements, striking improvement in consciousness, increased awareness and responsiveness, aphasic patients regained speech and comprehension. Only 2 of these maintained recovery. In 6 other patients, favorable responses were less dramatic, moderate but significant improvement in mentation immediately following HBOT, but definite neurologic dysfunction persisted, and immediately after decompression clinical picture reverted to pretreatment level. None of the remaining 12 patients improved during HBOT. | One patient developed hemolysis similar to that observed in tocopherol-deficient mice exposed to toxic levels of oxygen pressure. Jaundice and anemia occurred shortly after treatment, and blood pressure rose strikingly during procedure. Patient ultimately recovered from the anemia, but died 3 months later from complications of his cerebrovascular disease. | |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Holbach 1977[141] Germany (Poor) | Patients with cerebral infarction, including occlusive lesion of internal carotid or middle cerebral artery, TIA or completed stroke. | 1.5 atm x 40 minutes. TIA patients received one session. Stroke patients received 15 daily sessions. (Chamber type not reported) | None reported. | Time-series | 101: 27 TIA 38 complete stroke 36 chronic stroke |
| Holbach 1977[142] Germany (Poor) | Patients with internal carotid artery occlusion in chronic post-stroke state, with distinct neurologic deficits persisting beyond the 4th week following stroke. Internal carotid artery occlusion and the availability of a superficial temporal artery of sufficient caliber were determined by angiography. | 1.5 atm x about 40 minutes daily x 10-15. (Chamber type not reported) | Patients with superficial temporal artery of sufficient caliber were considered suitable to undergo EIAB if necessary. | Before-after | 20 |
| Imai 1974[105] Japan (Poor) | Patients with cerebral thrombosis. | 1.3 atm x 60 minutes daily x 5 sessions. (Monoplace chamber) | None. | Before-after | 18 |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Holbach 1977[141] Germany (Poor) | Neurologic exam and EEG. | Neurologic and EEG exams at beginning, middle, and conclusion of series of sessions. EEGs also during HBOT. |
| Holbach 1977[142] Germany (Poor) | Neurological exam. | Neurological exam given before and after each HBOT session. Patients assessed by an independent neurologist prior to HBOT treatment, during the course of treatment, at conclusion of treatment, and 6 weeks after conclusion of treatment or after EIAB. |
| Imai 1974[105] Japan (Poor) | Psychological and physical tests, Bender-Gestalt, memory scale. | Unclear if and when baseline conducted. Followup conducted after one or two sessions. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Holbach 1977[141] Germany (Poor) | Complete stroke due to occlusion of the internal carotid artery (23 patients): 72% had marked improvement of neurological deficit at conclusion of HBOT treatment.<br>Complete stroke due to middle cerebral artery occlusion (15 patients): 66% had a marked improvement of neurological deficit at conclusion of HBOT treatment.<br>Chronic stroke (36 patients): 45% had a marked improvement of neurological deficit at conclusion of HBOT treatment.<br>No neurological outcome data reported on patients with TIAs. | Not reported. | Neurologic exams not described, results of these reported in very general way. |
| Holbach 1977[142] Germany (Poor) | 11 patients (55%) favorably affected by HBOT all received EIAB after HBOT therapy complete; 9 patients (45%) affected little by HBOT (little or no improvement immediately after HBOT and 6 to 12 months later). | Not reported. | |
| Imai 1974[105] Japan (Poor) | Bender-Gestalt test and memory scale after 1 or 2 courses of treatment:<br>In 18 cases of cerebral thrombosis, orientation improved 20% or more, mental control and associate learning improved 10%-15%, visual reproduction, color recognition, body image improved 15%-20%, and logical memory, digit span, and story recall improved 1%-4%. Total score improved 15%-20%.<br>Aphasia, old memory, neurological signs improved, disturbance of recent memory not improved. | Not reported. | Results reported only ranges of percentage improvement. Unclear how subjects chosen. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Jain 1989[134] Germany (Poor) | Patients with cerebrovascular occlusive disease, age 44-64 years, with clinically assessible spasticity and radiographically documented diagnosis. | 1.5 atm x 45 minutes daily x 5 weeks. The first HBOT session was given without physical therapy, subsequent sessions conducted simultaneously with physical therapy. (Chamber type not reported, but HBOT occurred simultaneously with physical therapy, so assume multiplace) | Stroke rehabilitation, including physical therapy. Outpatient physical therapy continued after HBOT treatments completed. | Time-series | 21 |
| Jain 1990[143] Germany (Poor) | Patients with occlusive cerebrovascular disease and residual hemiparesis or hemiplegia, referred from acute-care stroke facilities. Stable chronic post-stroke state (3 weeks to 5 years) and no day-to-day neurological changes during the first week of admission to the clinic. Only patients who were available to senior author for clinical examination before, during, and after HBOT therapy are included in the paper. | 1.5 atm x 30 minutes daily x up to 5 weeks. (Chamber type not reported, but grip strength measured in the chamber, so assume multiplace) | Physical therapy simultaneously with HBOT. | Before-after | 25 |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Jain 1989[134] Germany (Poor) | Motor power of the hand using a hand-held dynamometer and measured in the paralyzed hand only (graded as 0-5). Spasticity assessed on a scale of 0-5. | Followup measurements of spasticity at 24 hours after each HBOT session. Timing of motor power tests not stated. Followup continued every 3 months. |
| Jain 1990[143] Germany (Poor) | Spasticity (graded 0 - 5), handgrip by dynamometer, neurological and functional assessment. | Assessments at admission and discharge, handgrip measured during first week of stay. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Jain 1989[134] Germany (Poor) | Of 21 patients: A rapid improvement of spasticity was noted in all the patients during the first HBOT session. This was significantly more than that observed with physical therapy, normobaric oxygen, or hyperbaric air. Improvement was transitory and receded during first 24 hours, but effects were more durable when physical therapy was carried out with HBOT and repeated daily for 5 weeks. Improvement maintained at 6 months to 1 year followup. Recovery of motor function was sometimes not detectable until after a few HBOT sessions. Recovery of motor function was slower but more durable. In patients with marked spasticity of lower extremities, improved gait resulted after "retraining" to walk. No change in tendon reflexes, clonus diminished.<br>(Grade changes are given for during HBOT, after 6 weeks of HBOT, and at 6 months to 1 year followup) | No complications. Two patients showed a transient tremor of the hand at the end of the session but this did not recur. | Results include only hand spasticity grades during, 6 weeks post, and 6-12 months post HBOT - no baselines and no motor power results. |
| Jain 1990[143] Germany (Poor) | All patients with spasticity grade 2-5 had spasticity reduced by 1 or 2 grades during HBOT. Improvement initially transient, regressed 1-8 hours after treatment, prolonged up to 12 hours by conducting physical therapy in chamber. Many patients kept their improvement at 3 months followup without additional HBOT treatments. | Not reported. | |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Kapp 1981[144] Florida (Poor) | Patients with angiographic evidence of carotid or middle cerebral artery occlusion, weakness on opposite side or speech impairment, and less than age 80. | 1.5 atm x 40 minutes daily x 14 days. (Chamber type not reported, used mask) | None reported. | Time-series | 22 |
| Li, 1998[135] China (Poor) | Patients with cerebral thrombosis at one hospital (390 male, 100 female, age 28-79), with disturbance of consciousness and cognition, aphasia, etc., confirmed by neurologist. | 2.5 atm x 90 minutes with a 15-minute break, daily. One course = 15 treatments. Patients usually had 3 to 4 courses, rarely more. (Chamber type not reported) | None reported. | Before-after | 490 |
| Neubauer 1980[139] Florida (Poor) | Consecutive patients with acute or chronic completed cerebrovascular accident: 34 acute, 88 chronic; mean age 66 (range 44-88). | For patients with onset of symptoms 4 hours or less: Pressure not specified. 60 minutes every 12 hours (some increased to every 2-6 hours). After 10 treatments, reduced to weekly, then monthly. Mean total treatments = 16 (range 12-20). For > 4 hours since onset of symptoms: 2.0 atm x 60 minutes daily x 10, then weekly x 4, then monthly thereafter. Average total treatments = 10 (range 10-90). (Monoplace used in all but 6 patients) | None reported. | Before-after | 122 |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Kapp 1981[144] Florida (Poor) | Neurological function, specifically grip strength, mental status, speech, 2-point discrimination, and repetitive thumb/finger movements. | Evaluation before, twice during, and after every HBOT treatment. |
| Li, 1998[135] China (Poor) | Evaluation: completely cured (signs & symptoms disappeared completely, patients lead normal, active lives without difficulty); markedly improved (most signs & symptoms disappeared, "myodynamia" improved more than 2 degrees); improved (symptoms & signs disappeared partially, some difficulty in walking, cannot care for self entirely, "myodynamia" improved less than 2 degrees); no effect (no improvement in signs & symptoms); not reported how these were measured or when, or by whom. | Not reported. |
| Neubauer 1980[139] Florida (Poor) | No standard tests; changes in ambulation reported for some patients based on assessments from neurologists, physical therapists, nurses, MDs, and family. Reported increased quality of life for some patients - measure not given. | Not reported. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Kapp 1981[144] Florida (Poor) | 10/22 (45%) had improved motor function during HBOT.<br>6/14 (43%) with infarction of left hemisphere with dysplasia had improvement in speech.<br>7/10 (70%) responders to HBOT subsequently had successful revascularization with no further cerebral infarcts from 4-20 months following surgery (3 had no or unsuccessful revascularization). | No complications definitely related to HBOT.<br>One patient developed pulmonary infiltrate after 5 days, 1 had a pulmonary embolus after 10 days. | Study intended to identify candidates for cerebral revascularization procedure. |
| Li, 1998[135] China (Poor) | 108/409 (26%) completely cured, 157/409 (38%) markedly improved, 166/409 (41%) improved, 59/409 (14%) no effect.<br>Also report: In a group receiving HBOT and conventional treatment 10/25 (40%) markedly improved, 15/25 (60%) improved. In a group receiving conventional treatment alone, 4/25 (16%) markedly improved, 19/25 (76%) improved, 2/25 no effect (8%). | Not reported. | |
| Neubauer 1980[139] Florida (Poor) | Treatment begun when patient bedridden (11 patients):<br>9% improved enough to use a wheelchair, 18% to walk with aids, 27% to walk independently, 45% no improvement.<br>Treatment begun when patient wheelchair bound (31 patients):<br>26% improved enough to walk with aids, 45% to walk independently, 29% no improvement.<br>Treatment begun when patient walking with aids (48 patients):<br>56% improved enough to walk independently, 44% no improvement.<br>49/79 (62%) who received HBOT 5 months-10 years after onset of stroke reported improvement in quality of life (increased ability to communicate with family members, willingness to participate in social activities, interest in constructive self-regulatory behavior).<br>Compared to patients with stroke at another hospital without HBOT, HBOT patients had fewer days in the hospital (HBOT 177 days vs standard treatment 287 days) | 5%-6% of patients developed barotrauma which was usually minor and easily controlled with medication (type not stated).<br>Myringotomies were required in 1% of patients. | Selection of comparison sample not defined. Very little discussion of differences for acute/chronic. Results presented for only 90 patients. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Noguchi 1983[136] Japan (Poor) | Patients treated with HBOT from April 1980 to March 1983 at one emergency medical center, 42.2% with central nervous system diseases which were probably due to systemic or local circulatory disturbances or hypoxia (cerebrovascular spasm, brain infarction, brain hypoxia, carbon monoxide intoxication, and spinal cord disease). | 2.0 to 3.0 atm x 45-60 minute (compressed within 20-25 minutes, decompressed over 5-30 minutes). Standard procedure was once daily, but twice daily was done at "critical stages, or in cases in which rapid improvement was expected." When symptoms became more stable, one treatment per day was done. Course was 3 weeks. (Multiplace) | None reported. | Before-after | 316 overall, 46 with cerebral infarction |
| Pilotti 1991[147] Italy (Poor) | Patients with clearly demonstrable completed stroke in the chronic phase, all had a stroke between 1977 and 1985 and received HBOT in 1985 at one research center. Control group recruited from neurology department at another hospital, matched for age at time of stroke, did not receive HBOT. | 1.5 - 2.0 atm x 90 minutes once daily x 30. (Chamber not reported, but reports patients are those reported in Marroni 1986, 1987) | No HBOT. | Retrospective comparison of cohorts | 65 HBOT 65 control |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Noguchi 1983[136] Japan (Poor) | Patients' response in the HBOT chamber, clinical signs and symptoms, clinical course, physical examination, and CT findings. Divided into marked improvement, improvement, and no improvement (not defined). When treatment was stopped too early to notice its effects, classified as "no improvement." GCS also used in cases of disturbance of consciousness. Cases recovered to 6-7 in GCS score were classified as "marked improvement," to 4-5 as "improvement," and to 3 "no improvement." | Not clear. |
| Pilotti 1991[147] Italy (Poor) | Patients in control and treatment groups were treated at 2 different institutions. Small differences with respect to age, sex, clinical history. Respiratory insufficiency, vascular insufficiency of inferior limbs, and arterial hypertension were higher in HBOT-treated group ($p < 0.05$) | Mortality 5 years post-stroke. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Noguchi 1983[136] Japan (Poor) | Of 46 cases of cerebral infarction: 21 (45.7%) marked improvement, 14 (30.4%) improvement, and 11 (23.9%) no improvement. | Not reported. | |
| Pilotti 1991[147] Italy (Poor) | Retrospectively examined mortality incidence in 5-year period after HBOT was received. | 21/65 deaths in HBOT group (32%), 31/65 in control group (48%) ($p$ = 0.048) | Not reported. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Saltzman 1965[145] North Carolina (Poor) | Patients with cerebral ischemia with neurologic deficits (hemiplegia, hemisensory loss, aphasia, and loss of consciousness). | 2.0 - 2.04 atm x less than 1 hour to 5 hours. Number of treatments not reported. (Chamber type not reported, used mask or head tent) | Myringotomies performed on most patients prophylactically. | Before-after | 25 |
| Steenblock 1998[137] California (Poor) | Patients with stroke (49) and brain injury (1). Mean age 61.8 (range 31-89). | 1.5 to 2.0 atm x 90 minutes daily 6 days a week. "Some" patients received treatment twice a day. Average total number of treatments = 55. (Monoplace) | Physical therapy 5 times per week and biofeedback therapy 5 times per week. | Before-after | 50 |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Saltzman 1965[145] North Carolina (Poor) | No standard test; changes in neurologic deficits described for each patient who improved either permanently or temporarily. | No baseline reported. Followup varies from patient to patient. |
| Steenblock 1998[137] California (Poor) | Patient self-evaluation of 16 functions graded ranging from "negative change" to "back to normal." Physical therapist evaluation of 33 functions (including range of movement, extremity strength, bed mobility, transfer, and balance) divided into "improvement," "no improvement," or NA if function was normal at baseline. | Patient evaluations prior to and after the series of HBOT, physical therapist evaluations prior to and at the "end of the program." |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Saltzman 1965[145] North Carolina (Poor) | Of 25 patients:<br>48% no improvement<br>32%: favorable responses during treatment, including cleared mentation & partial restoration of motor activity. However, definite neurologic dysfunction persisted, in most instances clinical picture reverted to pretreatment level immediately after decompression.<br>20% improved dramatically during treatment, with complete or almost complete restoration of neurologic & mental function, including immediate reversal of paralysis, within 5 to 10 minutes of beginning HBOT. In 2 of these, improvement was permanent. In 3, improvement dramatic but temporary, with return of symptoms 2 hours after HBOT. | One patient developed hemolysis. Jaundice and anemia occurred shortly after HBOT treatment, and blood pressure rose strikingly during procedure. | Difficult to know if TIA vs. stroke. 18 patients had onset of neurologic symptoms within 7 hours of starting HBOT. |
| Steenblock 1998[137] California (Poor) | At end of program, 96.7% of patients reported total improvement in at least one of the 16 functions. 3.3% reported no improvement, 30% considered the program "good," 46.7% considered program "excellent," 20% considered program "stupendous." Physical therapist evaluations found all patients showed one or more improvements among the 33 functions: 10% minimal gains, 7% mild gains, 48% good gains, 34% excellent gains.<br>Patients reported chronically cold arm or leg changed to warm during therapy. Fingernails and hair began to grow normally again, chronic fatigue generally relieved by the program. | "Only insignificant problems were encountered." Three of over 500 patients overall required tympanostomy tubes placed. | Exact timing of followup assessments not clear. One subject included had a diagnosis of "car accident". |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Population | HBOT protocol (Type of chamber) | Other interventions | Study design | Number of patients |
|---|---|---|---|---|---|
| Tsuro[138] 1983 Japan (Poor) | Part 1: patients with ischemic cerebrovascular disease, average age 50, neurological signs marked in 15, moderate in 9, and slight in 6.<br><br>Part 2: patients who developed mental signs lasting more than 2 weeks following surgery for cerebral aneurysm; 53% operated on within 2 weeks of subarachnoid hemorrhage, 47% later than 2 weeks after attack. | Part 1: 2.0 atm x 60 minutes daily x 6 to 30 times (average 13).<br><br>Part 2: 2.0 atm x 60 minutes daily, number of treatments not specified.<br><br>(Monoplace) | None reported. | Before-after | part 1: 30; part 2: 49 |
| Wassman 1986[146] Germany (Poor) | Completed stroke patients (74% male) who showed definite increase of EPE (electrical power equivalent) values after an HBOT series. All had persisting neurological deficits about 3 months after stroke as a result of occlusion of an internal carotid artery. | 1.5 atm x about 40 minutes, once daily x 10 to 15 treatments. (Chamber type not reported, states "specially constructed") | None reported. | Time-series | 73: 38 had EIAB surgery following HBOT series 35 did not |
| Zhou Shn-rong 1995[110] China (Poor) | Men & women age 1 month - 73 years, in coma due to acute cerebral ischemia & hypoxia in 95 cases: drowning (23), hanging (44), electric shock (2), narco-operation accident (14), Adam-Stoke's Syndrome (1), barbital poisoning (4), asphyxia (2), and cover-bedding syndrome (11). 3 cases head trauma, 226 carbon monoxide poisoning, 12 acute hydrogen sulfide poisoning. | 2.0-2.5 atm x 2 hours twice daily in the first 2 to 3 days, and then 2.0 atm once daily. Timing of treatment depends on change in patient's condition. Course of treatment may reach 40-60 treatments. (Chamber type not reported) | Not reported. | Before-after | 336 |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Outcomes measured | Baseline and followup |
|---|---|---|
| Tsuro[138] 1983 Japan (Poor) | *Part 1:* Neurological signs (motor, sensory, amnestic aphasia, hemiparesis) *Part 2:* Severity of mental signs classified into 4 grades: absent (no mental signs), slight (slight disturbance of mental signs, for example slight disturbance in recent memory), moderate (moderate disturbance of mental signs, presumed to have trouble in social life), and marked (marked disturbance of mental signs, not able to return to previous social life). Efficacy of HBOT ranked into 4 groups: excellent (improvement by 2 grades), moderately improved (improvement by 1 grade), slightly improved (improvement without promotion to higher grade), and unchanged (no change). Method of determining grades not specified. | Not reported. |
| Wassman 1986[146] Germany (Poor) | EEG, changes in motor function. | Neurological examinations carried out before, during, and after HBOT therapy. Patients followed for 4.5 years after HBOT or after EIAB surgery. |
| Zhou Shn-rong 1995[110] China (Poor) | Criteria for treatment effect: cure (consciousness and labor ability recovered with no sequelae, curative effect is stable during followup); notable effect (consciousness and labor ability recovered, with low-grade sequelae); improvement (consciousness recovered, patient can take care of self partly and has sequelae); no effect (patient's condition has no improvement or deterioration). Not reported how or when assessed. | Not reported. |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 6. Stroke observational study data (continued)

| Author, year, location (Quality) | Results | Adverse effects | Comments |
|---|---|---|---|
| Tsuro[138] 1983 Japan (Poor) | Part 1: 8/30 (27%) excellent recovery; 9/30 (30%) moderate improvement; 8/30 (27%) slight improvement; 3/30 (10%) unchanged neurological signs.<br><br>Part 2: 3/49 (6%) excellent improvement, 23/49 (47%) moderate improvement, 15/49 (31%) slight improvement, 8/49 (16%) unchanged. | Part 1: No patient showed aggravation of neurological signs after HBOT, Part 2 none reported. | |
| Wassman 1986[146] Germany (Poor) | 6 months after HBOT, both groups showed increases of 4 points in recovery from motor deficit. After bypass surgery (3-6 months after HBOT?), patients who had surgery showed an additional improvement of nearly 3 points during the next 8 months. This level of improvement continued in most patients during the remaining 3 years of the followup period. | States in 10,000 HBOT sessions conducted since 1967, no complications worth mentioning occurred. | |
| Zhou Shn-rong 1995[110] China (Poor) | Of 95 cases of cerebral ischemia and hypoxia: 68% cured, 2% notable effect, 4% improvement, 24 (25%) no effect. Of 3 traumatic brain injury: 100% regained consciousness after 7 to 20 HBOT treatments. | Not reported. | |



HBOT=hyperbaric oxygen therapy; atm=atmospheres; TIA=transient ischemic attack; EEG=electroencephalogram; EIAB=extra- intracranial arterial bypass; GCS=Glasgow Coma Scale; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| ***Patients with traumatic brain injury*** | | | | |
| Barrett 1998 | Patients with chronic stable TBI, at least 3 years post-injury. Controls = healthy volunteers for CBF measurements after one HBOT session. | Meeting abstract | Not reported. | 1.5 atm x 60 minutes x 120 sessions. 5 month rest between first 80 sessions and final 40 sessions. |
| Gelety 1983 | Patients in chronic coma from closed head injury. In vigil coma for 3 weeks-27 months, age 3-67 years. | Meeting abstract | Not reported. | 1.5 - 2.0 atm x 60 to 90 minutes x 40 to 80 treatments. |
| Guo 1996 | Patients with post-traumatic brain injury (26 male and 5 female). Manifestation of disease was intellectual stimulation and "hypomnesis". | Meeting abstract | Not reported. | Under 2.5 atm x 40 minutes twice with a break of 10 to 20 minutes in between, daily x 20 days. |
| Jianhui 2000 | Patients with brain stem damage without cerebral hernia, unconscious. GCS grade 4 to 7. | Conference proceedings | Not reported. | 2.0 atm x 80-90 minutes once daily x 10 per course x 1 to 6 courses, varying according to patient's condition. |
| Kondratenko 1981 | Patients with severe craniocerebral injury. | Meeting abstract | Not reported. | 1.90-1.45 atm x 30-60 minutes. Number of sessions depended on patient's condition. |
| Neubauer 2001 | Patients with varying degrees of TBI, age 3 to 80. Onset since injury: 6 months to 16 years. GCS 3-12. | Conference proceedings | Not reported. | Most received 1.5 atm x 60minutes, but those with seizure disorder received 1.1 to 1.25 ata. From 80 to 500 consecutive treatments. (monoplace chamber) |



HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| ***Patients with traumatic brain injury*** | | | | | |
| Barrett 1998 | None reported. | Controlled trial | 5 HBOT<br>6 control (no TBI) | Cerebral blood flow, speech fluency, neurologic, cognitive, and progressive exercise testing. | Not reported. |
| Gelety 1983 | None reported. | Before-after | 16 | Glasgow Coma Scale. | Not reported. |
| Guo 1996 | None reported. | Before-after | 31 post-traumatic brain injury. | Digital symbol test (from Wechsler adult intelligence scale). | Outcome measured pre- and post- therapy, but timing not specified. |
| Jianhui 2000 | Control group received routine therapy, including dehydration, antibiotics, cortex hormone, etc. | Controlled trial | 32 HBOT<br>25 control | GCS grade; cure (consciousness, symptoms disappear, can care for self), marked effect (consciousness, main symptoms disappear, can care for self on the whole, accompanying sequelae), positive effect (consciousness, on the mend, cannot care for self), no effect (still not conscious), death. | Not reported. |
| Kondratenko 1981 | None reported. | Before-after | 101 | Mortality. | Not reported. |
| Neubauer 2001 | All modalities of PT, OT, speech therapy, biofeedback, nutritional counseling, accupunture, herbal medications when indicated. | Before-after | 60 | Removal of G-tube, closing of tracheostomy, and communication ability. | Not reported. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| ***Patients with traumatic brain injury*** | | |
| Barrett 1998 | In the HBOT group, no changes were seen in progressive exercise and neurologic testing. Speech fluency universally improved, as did group mean scores of memory, attention, and executive function. Improvement peaked at 80 treatments. (no scores given, scales used not given, p values not given) | |
| Gelety 1983 | 10/16 cases responded (63%); 6 were successfully rehabilitated and 4 had a lightening of the coma and became semi-responsive; 6 showed no change, there was no worsening in any patient. | |
| Guo 1996 | Change in digital symbol test (post test mean-pre test mean):<br>cerebral thrombosis: 6.1 (+/- 5.5) (14.7-8.6)<br>$p < 0.0001$ | See stroke section for stroke results |
| Jianhui 2000 | HBOT group: 22/32 (69%) cure, 4/32 (13%) marked effect, 0/32 (0%) positive effect, 1/32 (3%) no effect, 5/32 (16%) death.<br>Control group: 9/25 (36%) cure, 3/25 (12%) marked effect, 1/25 (4%) positive effect, 2/25 (8%) no effect, 10/25 (40%) death.<br>$p < 0.05$ (for all comparisons? Not clear)<br>Return to consciousness by 2 weeks: 18/32 (56%) HBOT, 4/25 (16%) control. ($p$ not given) | |
| Kondratenko 1981 | For patients with craniocerebral injury in the acute period, favorable effect observed in 69% of cases, mortality decreased by 38.1% as compared to the control group. No uniform effect of HBOT was obtained in both groups in the rehabilitation period. | |
| Neubauer 2001 | In nearly all cases the G-tube was removed, in 80% the tracheostomy was closed. Few with GCS at lower level returned fully to society. 70% some degree of improvement to point of being able to communicate verbally, with word-board, computer or sign language. No patient regressed. | |



HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| Rockswold 1985 | Patients with head trauma at one medical center. | Meeting abstract | Unable to obey commands or pronounce recognizable words. | Not reported. |
| ***Patients with other brain injury*** | | | | |
| Harch 1994 | Patients with chronic traumatic, ischemic, hypoxic, and anoxic brain injuries. | Meeting abstract | All referrals with chronic stable encephalopathies manifested by perfusion/ metabolism deficits on HMPAO SPECT scans that improved on repeat scan immediately after a 1.5 or 1.75 ata/90 min HBOT treatment. | Primarily 1.5 atm x 90 minutes once or twice daily x 40 (1 patient), 60 (1 patient), or 80 (16 patients) treatments. |
| Juan 1992 | Patients with congenital heart diseases who had anoxic encephalopathy after open heart surgery done under extracorporeal circulation. Age 3 to 16 years; time in coma was 30, 35, 9, and 12 days. | Meeting abstract | Not reported. | Dose, total number of treatments not reported. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Rockswold 1985 | All patients receive intensive neurosurgery care, treatment group also receives HBOT. | Randomized controlled trial | 30 (first admitted into the study) | Intracranial pressure, neurological exams, CT scans of the brain, multimodal evoked responses, neuropsychological tests, and neurological followup evaluations. This abstract reports mortality data only on the first 30 patients. | Monitored during hospital and post-hospital course (not specified). |
| ***Patients with other brain injury*** | | | | | |
| Harch 1994 | Standard rehabilitation when possible. | Before-after | 18 | Neurologic changes were noted by combinations of history, exam, video, occupational and physical therapists, neuropsychologists, referring doctors, and final SPECT scans. | Not clear. |
| Juan 1992 | None reported. | Time-series | 4 | Regained consciousness, intelligence, and limb function (not specified how measured). | Not reported. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| Rockswold 1985 | Mortality rate of those with GCS score of 7-9 show no significantl difference between groups; patients with GCS of 3 had 100% mortality rate. Patients with GCS of 4-6 results suggest increased survival among HBOT-treated group (p = 0.100). | Numbers of patients in each group are not given, states that number with GCS 4-6 is "small". |
| ***Patients with other brain injury*** | | |
| Harch 1994 | 18/18 patients (100%) showed motor, behavioral, personality, or cognitive gains. 6/18 patients (33%) noted neurological changes on the intervention either in chamber or later that day, 16/18 (89%) noted neurological changes by 18 treatments (range 7-33) including emotional lability and personality changes. All noted changes by 40 treatments, many had further gains at 60-70, and all were improved at 80 treatments. 16/18 patients (89%) or their parents requested continuous treatment beyond the study endpoint of 80 treatments, 2 patients (11%) (40 and 60 treatments) stopped for personal reasons and sinusitis. | |
| Juan 1992 | 4 patients (100%) regained consciousness on 6th, 2nd, 10th, and 4th HBOT treatment, respectively. They walked without help on the 50th, 10th, 20th, and 20th treatment. 3 (75%) had perfect intelligence restored on the 30th, 25th, and 20th treatment, 1 (25%) had partial intelligence restored after 10 treatments and then stopped treatment for some reason. | |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| Keim 1997 | Patients age 4-72 with brain injury from carbon monoxide (4 patients), closed head trauma (4 patients), and ischemia/asphyxia (2 patients). | Meeting abstract | Not reported. | 2.0 atm x 90 minutes or 1.5 atm x 90 minutes (not specified which patients had which treatment) for time intervals determined by clinical course or IRB protocol (maximum 120 treatments over 390 days). Time interval from injury to treatment ranged from 6 hours to 11 years. |
| Lantsev 1981 | Newborn infants with asphyxia delivered by Caesarian section. | Meeting abstract | Not reported. | 3.0 atm x first 15 minutes, then 1.5-1.3 atm x 1.5-2 hours. Started within 5 minutes after birth. |
| Lianbi 2002 | Children with brain injury (23 post-operation for cerebral tumor, 39 with cerebral trauma), average age 6.5 years (5.4), all with severe or moderate cerebral edema, in coma 3-12 days. | Conference proceedings | Not reported. | 0.2 Mpa once daily, average number of treatments was 30. |
| Mathieu 1982 | Patients admitted to one emergency unit for unsuccessful hanging between 1970 and 1981. | Meeting abstract | Not reported. | 136 patients had 278 HBOT courses at 2.0 atm x 90 minutes. 34 patients with only minor neurological troubles received normobaric oxygen. |



HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Keim 1997 | None reported. | Before-after | 10 | Clinical improvement, SPECT imaging. | Not reported. |
| Lantsev 1981 | Artificial pulmonary ventilation. | Before-after | 56 | | 3-10 year followup. |
| Lianbi 2002 | None reported. | Time-series | 62 | Neuropediatric and neurophysiologic evaluation, change in functional outcomes. | Before treatment and at 1, 2, and 3 months after HBOT. |
| Mathieu 1982 | All had supportive and anticerebral edema measures. | Before-after | 170 (136 received HBOT, but results are reported for entire group) | Mortality, survival without sequelae, survival with neurologic sequelae. | Not reported. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| Keim 1997 | Clinical improvement was seen in all 10 patients (100%). | |
| Lantsev 1981 | 33 infants delivered by caesarian section followed for 3-10 years. Only in one child (3%), at age 3 1/2, epilepsy and deaf-mutism were revealed. The other children (97%) developed normally. | |
| Lianbi 2002 | Satisfactory curative effect was observed in all patients (100%), especially within the early time of lesion (sooner after injury?), results are invariable and permanent, no evidence that HBOT promoted growth or metastasis of tumor. | |
| Mathieu 1982 | 132/170 (78%) recovered completely without any sequelae, 8/170 (5%) recovered with neurological sequelae, and 30/170 (17%) died. Neurological recovery was obtained after 0.8 HBOT course in patients in grade I coma, 1.5 courses in patients in grade II, 2.5 courses in grade III, and 3.9 courses in grade IV. In any case, recovery was obtained after the fifth course. Results were significantly better when HBOT treatment began before the third hour after the unsuccessful hanging. | Same study as Wattel 1981 with one more years' data, more patients |



HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| Pilinoga 1981 | Neonates with intracranial birth injuries. | Meeting abstract | Not reported. | 1.2-1.5 atm x 20-30 minutes; number of sessions depended on severity of neonate's state, range 5-12 sessions. Started 3-9 days after delivery. |
| Yi Zhi 1996 | Patients with persistent vegetative state from head injury, cerebral hemmorhage, cerebral infarction, surgery for meningioma. Longest coma lasted 281 days prior to HBOT. | Meeting abstract | Not reported. | 0.2 Mpa x 80 minutes per session, with a break of 10 minutes, one session per day. One treatment course was 10 sessions. Minimum sessions 20 and maximum 86. |
| ***Patients with cerebral palsy*** | | | | |
| Barrett 2001 | Children with cerebral palsy, average age 41.8 months. | Meeting abstract | Not reported. | 1.5 atm x one hour daily x five days per week x 60 treatments. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Pilinoga 1981 | None reported. | Time-series | 80 infants with intracranial birth injuries received HBOT (48 severe, 21 moderate, 11 mild). 52 followed up 6 months to 6 years. | Elimination of pathological disorders in respiration, cardiovascular, thermal regulation, and regression of neurological impairments, observation by pediatrician and neuropathologist after discharge from hospital. | 6 months to 6 years followup. |
| Yi Zhi 1996 | Conventional therapy. | Before-after | 8 | Resumed consciousness. | Not reported. |
| ***Patients with cerebral palsy*** | | | | | |
| Barrett 2001 | None reported. | Before-after | 5 (results on 4 only, one patient dropped before completion) | Modified test of gross motor and fine motor function (GMFM-m) and modified Ashworth Spasticity Scale. | Outcomes measured before and after HBOT therapy. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; CBF=cerebral blood flow; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ= memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| Pilinoga 1981 | Functions of cardiovascular system and thermal regulation reached usual age norms following 2-3 HBOT sessions. Neurological symptoms regressed at a slower rate depending on severity of intracranial birth injuries. Of 52 children under observation from 6 months to 6 years found no deviations from the age norm. | |
| Yi Zhi 1996 | All 8 patients (100%) resumed consciousness upon completion of the HBOT courses. | |
| ***Patients with cerebral palsy*** | | |
| Barrett 2001 | Modest decreases in spasticity and improvements in the modified GMFM scores for all patients completing the study. | |



HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| Kazantseva 2002 | Children under age 14 with brain injury (47 hypertensive headache, 25 epilepsy, 8 cerebral palsy). | Conference proceedings | Not reported. | HBOT: 1.2 atm x 20 minutes x 1-4 sessions (47 children); MHT (minimized hyperbaric treatment): 1.05-1.1 atm with 30% oxygen x 20 minutes x 5-10 sessions (54 children, 40 of them received Q10 10-30 mg and picnogenol 15-30 mg). 21 children received HBOT and later were administered MHT. |
| Lobov 2002 | Children age 6 months to 15 years with various forms of clinical cerebral palsy. | Conference proceedings | Not reported. | "The whole spectra of mild standard isopressure regimens" up to 2.0 atm with 40-60 minute exposures, the whole course lasting 1-10 exposures. |
| Marois 1998 | Children with cerebral palsy, with a functional diagnosis of spastic diplegia, 10 girls and 15 boys, mean age 5.6 years, range 3.1-8.2 years. | Abstract (there is reference to a website that may contain full results, but is no longer available). | Not reported. | 1.75 atm x 60 minutes x 20. |
| Zerbini, 2002 | Children with chronic encephalopathy. | Conference proceedings | Not reported. | Not reported. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Kazantseva 2002 | 40/54 MHT children received Q10 10-30 mg and picnogenol 15-30 mg. | Retrospective cohort | 80 | Neurological exam. | Not reported. |
| Lobov 2002 | None reported. | Before-after | 60 | Clinical improvement. | Not reported. |
| Marois 1998 | None reported. | Time-series | 25 | The same evaluators (physician, physical and occupational therapist) conducted pre and post evaluations. Gross Motor Function Measure, Jebsen Test for hand function, modified Ashworth Scale (evaluation by both physical therapist and physician), evaluation of reflexes. | Evaluations before treatment and at 2 weeks post-treatment and 3 months post-treatment. |
| Zerbini, 2002 | None reported. | Before-after | 232 | Spasticity, global motor coordination, attention, memory, comprehension, reasoning, interest, visual perception, control of the sphincter, control of the sialorrhea (?), increasing sociability. | Evaluated 1-6 months after HBOT. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| Kazantseva 2002 | Minimized hyperbaric treatment accompanied by a more pronounced therapeutic effect than HBOT. Use of antioxidants noticeably increased the efficacy of HBOT and duration of the after effect period. | Results of neurological exam not reported, only intermediate outcomes. |
| Lobov 2002 | Good or satisfactory outcome up to clinical convalescence was obtained in 20 patients with hypoxic-and-dyscirculatory cerebral lesions. Results insignificant or doubtful in 30 patients (50%). Efficacy of HBOT depended on disease severity and patient's age. Better results in children under 1 year, at risk of cerebral palsy development, and in those with spastic hemiplegia and diplegia. | |
| Marois 1998 | Results of 3-month follow up evaluation not available at time of publication.<br>Pre and post-treatment (2 weeks):<br>GMFM significantly improved for items B,D, and E ($p$ <0.001); Jebsen Test significant for card turning, lifting objects, and stacking checkers ($p$ < 0.05); spasticity decreased in the hip abductors, hamstrings, and ankle plantarflexors for the evaluation by physician (p < 0.01); spasticity decreased in quadriceps as measured by the physical therapist ($p$ < 0.05); patellar tendon and Achilles tendon reflexes significantly reduced ($p$ < 0.05); questionnaire revealed significant improvement for walking and sitting ($p$ < 0.01) and knee walking ($p$ < 0.05). | |
| Zerbini, 2002 | 41.8% had decrease in spasticity, 33.2% improved global motor coordination, improvement in attention 40.1%, memory 10.8%, comprehension 13.3%, reasoning 5.6%, interest 6.9%, visual perception 12.9%, control of the sphincter 6.5%, control of the sialorrhea 4.3%, which made it possible to improve daily activities, increasing sociability in 13.8% of cases. | |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| ***Patients with stroke*** | | | | |
| Guo 1996 | Patients with cerebral thrombosis (24 male 16 female). Manifestation of disease was intellectual stimulation and "hypomnesis". | Meeting abstract | Not reported. | Under 2.5 atm x 40 minutes, twice with a break of 10 to 20 minutes in between. Every day x 20 days. |
| Holbach 1979 | Stroke patients with persisting neurological deficits due to occlusive lesions in the internal carotid or middle cerebral artery. | Meeting abstract | Not reported. | All patients received 15 single HBOT sessions given daily (dose/duration not reported) before either surgical treatment (extra-intracranial arterial bypass) or medical treatment. |
| Jain 1988 | Post-stroke with no day-to-day changes in neurological status despite physical therapy. | Meeting abstract | Not reported. | 1.5 atm x 60 minutes x 1 |
| Jain 1989 | Patients in chronic post-stroke stage with severe spasticity of the hemiplegic side. | Meeting abstract | Not reported. | Normobaric 100% oxygen, hyperbaric air, and HBOT at 1.5 atm, duration not clear (40 minutes daily for 5 weeks?). |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| ***Patients with stroke*** | | | | | |
| Guo 1996 | None reported. | Before-after | 40 | Digital symbol test (from Wechsler adult intelligence scale). | Outcome measured pre- and post- therapy, but timing not specified. |
| Holbach 1979 | Surgery or medical treatment. | Randomized controlled trial (randomized to either surgery or medical treatment, after all received HBOT) | 112 | Improvement, favorable EEG or neurological response (not described). | Long-term neurological and EEG analytical exams regularly carried out (not specified when). |
| Jain 1988 | None reported. | Before-after | 4 | The patients were accompanied into the HBOT chamber and had motor power (hand grip) and spasticity measured manually by the author. | Baseline not reported, followup varied, up to two weeks post-treatment |
| Jain 1989 | Physical therapy. | Before-after | 18 | Clinical and video-recording of the gait, dynamography, and photography of the spastic hand. | Spasticity measured during HBOT treatment, effect of physical therapy was observed both prior to and during HBOT. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| ***Patients with stroke*** | | |
| Guo 1996 | Change in digital symbol test (post test mean-pre test mean): cerebral thrombosis: 12.2 (+/- 5.5) (28.6-16.4) $p < 0.0001$ | See brain injury section for traumatic brain injury results. |
| Holbach 1979 | Nearly all patients with a favorable EEG or neurological response, or both, to HBOT showed a positive response to extra-intracranial arterial bypass surgery, while in patients where HBOT was considered to be ineffective there was little or no change in impaired neuronal functions following surgery. | Both groups received HBOT, study designed to assess HBOT as predictor of surgical success |
| Jain 1988 | 3 patients with spasticity: relief of spasticity which was maximal 15 minutes after start of HBOT and the effect persisted on average 1 hour following the session. During this period motor function improved. Range of motion of the limbs and finger movements on the paralyzed side improved, and posture of the hand improved. In one patient in which handgrip was measured, it increased from 2 to 4 kg during the first session, and 2 weeks later handgrip was 12 kg. In one patient with no spasticity, grip increased from less than 1 kg to 4 kg during the first session and dropped to 2 kg one hour later. No change in tendon reflexes. Improvement in motor power was observed again in the following HBOT session and improvement to 4 kg maintained for the rest of the day. | Results reported on a per-patient basis. |
| Jain 1989 | Maximum relief was seen under HBOT in all patients. Improvement was transient initially but combined HBOT and physical therapy for 40 minutes daily for 5 weeks led to persisting improvement of spasticity and contributed to improvement of motor function. | |



HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| Nagayoshi 1991 | Patients with cerebral embolism treated with HBOT from 1981 to 1989. | Meeting abstract | Not reported. | Dose, duration not reported, patients analyzed according to period when HBOT was started from onset of disease (0-24 hours, 24-48 hours, 48-72 hours, 3 days-1 week, 1-2 weeks, 2-3 weeks, and 3-4 weeks). |
| Oshima 1990 | Patients with acute cerebral infarction, admitted to one hospital within 2 weeks of onset. | Meeting abstract | Not reported. | 2.0 atm x 90 minutes once daily, and in severe cases, twice daily. 20-30 sessions. |
| Sansone 1997 | Patients with focal cerebral ischemia due to occlusion of middle or anterior cerebral arteries. Mean age 61 (range 43 - 76). | Meeting abstract | Not reported. | HBOT=100% oxygen at 1.5-1.8 atm x 60 minutes daily (3x20 minutes separated by 3 minutes of breathing air) daily x 8-10 treatments. Control =room air x 60 minutes daily (3x20 minutes separated by 3 minutes of breathing air) daily x 8-10 treatments. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Nagayoshi 1991 | None reported. | Before-after | 158 | Consciousness, motor, sensory, speech, and other "subjective symptoms." Each item evaluated on 4-point scale, improvement rate classified as excellent, good, fair, or poor. | Before treatment and after 20 treatments |
| Oshima 1990 | None reported. | Controlled trial? | 67 (26 mild, 21 moderate, 20 severe). Patients in each severity group divided into 2 groups with or without HBOT, but numbers in each group not given. | Lactic acid of cerebrospinal fluid, CT of the brain, infarction index (size of maximum forcus/hemicerebral space X 100), clinical symptoms. | Outcomes measured before, during, and after therapy (not specified). |
| Sansone 1997 | None reported. | Randomized controlled trial | 17 (9 intervention, 8 control) | Neurologic Recovery Score (assume 10 = no disability, 0 = dead, but unclear due to typographical error in report). | Baseline, 6 and 12 months |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| Nagayoshi 1991 | In groups that started within 48 hours, rates of excellent and good cases were higher than any other group ($p$ <0.05). | |
| Oshima 1990 | Effects of HBOT were remarkable in the moderate group, effects were not significant in mild or severe group. Improvement of clinical symptoms correlated with decrease in lactic acid of cerebrospinal fluid and infarction index. | |
| Sansone 1997 | Difference in neurological recovery score (10= no disability, 0 = dead), (HBOT-Control)<br>6 months: -0.8 (sd 0.9), $p$ = 0.21<br>12 months: -2.2 (sd 1.0), $p$ = 0.031 | Does not give baseline data, only reports change in score within group, not compared to change in control group. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Population | Type of publication | Inclusion criteria | HBOT protocol |
|---|---|---|---|---|
| Shalkevich 2000 | Patients with ischemic stroke. | Meeting abstract | Not reported. | HBOT: 1.5 atm x 40-60 minutes x 4-6 procedures. HBOT applied once every 6 months. Control no HBOT. |
| Vysotsky 1981 | Patients with air embolism of the cerebral vessels developing mainly during open heart surgery, and patients with thrombosis and thromboembolic complications. | Meeting abstract | Not reported. | Patients with air embolism (17): 6-8 atm for 40-35 minutes. "On subsequent stepwise regression beginning at 3-2.8 atm artificial ventilation of the lungs with 100% oxygen while under pressure" Patients with thrombosis (7): intermittent HBOT of 6 sessions at 3 atm for 60 minutes. |
| Ystrokeu 1981 | Patients with ischemic stroke and cerebral injuries and intracranial hematomas. Most were in grave condition in coma and stupor and severe focal symptoms. | Meeting abstract | Not reported. | 1.6-2.0 atm x 40-60 minutes x 6-15 sessions. Treatment started in 80% of cases on day 2-7 after onset, in 20% on day 7-20. |
| Yu 1981 | Patients with ischemic stroke and cerebral injuries and intracranial hematomas. Most in critical condition with coma and stupor with severe focal symptoms. | Meeting abstract | Not reported. | Course: 4 sessions at 1.6-2.0 atm x 40-60 minutes x 6-15 treatments. Started on 2nd-7th day after insult in 80%, 7th-20th day in 20%. |
| Zhem 1986 | Patients age 40-70 with cerebral thrombosis. | Meeting abstract | Not reported. | Not reported. |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Other interventions | Study design | Number of patients | Outcomes measured | Baseline and followup |
|---|---|---|---|---|---|
| Shalkevich 2000 | Both groups received low-dose aspirin, antihypertensive and antisclerotic agents. | Controlled trial | 48 treatment, 49 control | Recurrent stroke/TIA. | 5 years of followup. |
| Vysotsky 1981 | None reported. | Before-after | Says 32 patients studied, but report on only 24. | Recovery of consciousness, focal neurological symptomatology. | Not reported. |
| Ystrokeu 1981 | None reported. | Before-after | 264 (140 ischemic stroke;124 cerebral injuries and intracranial hematomas) | Neurological symptoms, specifics or how measured not reported (also reports other clinical data, such as cerebral blood flow). | Not reported. |
| Yu 1981 | None reported. | Before-after | 140 stroke, 124 cerebral injuries and intracranial hematomas. | Neurological symptoms. | Not reported. |
| Zhem 1986 | None reported. | Before-after | 36 | Short-term memory (MQ of individual event scale, observation of the character of memory function in different hemispheres). | Not reported- results "after treatment by HBOT." |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 7. Conference proceedings and abstract-only study data (continued)

| Author year | Results | Comments |
|---|---|---|
| Shalkevich 2000 | Within 5 years, rare TIA in 2 patients (4.8%) in HBOT group, in the arterial system where a stroke previously occurred, in control group, 3 patients (5.9%) had a recurrent stroke, 2 within 2 years and 1 within 4 years. | No data on baseline severity or risk factors, selection of patients into HBOT/no-HBOT not described. |
| Vysotsky 1981 | Consciousness returned in 13/24 (54%) patients in Group 1 (air embolism). In Group 2 (thrombosis), 1/6 patients (17%) regained consciousness. Focal neurological symptomatology regressed much more slowly. | |
| Ystrokeu 1981 | In patients with ischemic strokes, 80% had a regression of neurological symptomatology (i.e., symptoms improved) and in 52% of observations the onset of diminishing neurological deficiency coincided with the beginning of the HBOT course. Data on neurological symptoms in patients with brain injury not reported. | Notes "sporadic convulsive fits." |
| Yu 1981 | Neurological symptoms regressed in 80% of patients with ischemic stroke and in 52% the onset of improvement coincided with the start of HBOT. | |
| Zhem 1986 | After HBOT treatment, memory of patients improved significantly, MQ of individual event scale value, $p < 0.001$ (no details given) | |

HBOT=hyperbaric oxygen therapy; TBI=traumatic brain injury; atm=atmospheres; GCS=Glasgow Coma Scale; GMFM=Gross Motor Function Measure; HMPAO SPECT=99mTc-hexamethyl propylene-amine-oxime single photon emission computed tomography; MPa = miliPascals TIA=transient ischemic attack; MQ=memory quotient; MHT=minimized hyperbaric treatment; PT=physical therapy; OT=occupational therapy; CT=computerized tomography

## Evidence Table 8. Quality assessment of controlled studies

| Author, year (Quality) | Randomization/ allocation concealment | Baseline comparability | Timing of baseline measures sufficiently close to intervention? | Intervention the same for all patients within groups? | Outcome measures stated and objective? |
|---|---|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | | | |
| Artru 1976[88] (Fair) | Randomization, allocation methods not reported. | Similar. | Yes (coma scored at admission to study) | No, other medical factors delayed or disrupted treatments. | Yes (mortality and duration of coma, pulmonary complications) |
| Rockswold 1985,[89] 1992,[90] 1994[91] (Fair) | Randomization, allocation methods not reported. | Small differences in proportion with operable mass lesions, multiple trauma, elevated ICP and "poor outcome BAEPs (Brainstem Auditory Evoked Potentials) and SSEPs (Somatosensory Evoked Potentials )" | Yes | No, number of treatments could vary. | Yes |
| ***Studies of other types of brain injury*** | | | | | |
| Jianhua 1995[106] (Poor) | Randomization, allocation methods not reported. | No statistical test performed, but baseline characteristics reported, appear similar. | Not stated | Similar HBOT treatments (not exactly the same). Control interventions actually used not stated. | Stated, but not objective |
| ***Studies of cerebral palsy*** | | | | | |
| Collet 2001[119] (Fair) | Yes, centralized randomization, concealment by sealed envelopes. | Some differences in presumed cause and type of CP and in baseline GMFM scores. | Yes | Yes | Yes (GMFM) |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Timing of follow-up measurements stated and adequate? | Followup adequacy (loss to followup) | Handling of dropouts or missing data | Masking | Statistical analysis |
|---|---|---|---|---|---|
| ***Studies of traumatic brain injury*** | | | | | |
| Artru 1976[88] (Fair) | Yes (1 month) | All 60 followed for 12 months | No dropouts. | Not reported | Chi-squared test presented for some outcomes. |
| Rockswold 1985,[89] 1992,[90] 1994[91] (Fair) | Yes | Good; 1 lost to follow up | Unclear - 24 protocol violations occurred, including medical condition not compatible with study and/or HBOT, but unclear how these handled. Two missing data in control group, lost to followup and excluded from analysis. | Single masked. Assessments done by masked neurologist | Stratified chi-squared analyses by GCS score and age, comparisons based on 12-month followup exam. Chi-squared test and survival analysis presented for some outcomes. |
| ***Studies of other types of brain injury*** | | | | | |
| Jianhua 1995[106] (Poor) | Not stated | Dropouts not reported | Dropouts not reported. | Not reported | Groups had "obvious differences ($p<0.001$) through the processing of statistics," no details. |
| ***Studies of cerebral palsy*** | | | | | |
| Collet 2001[119] (Fair) | Yes (3 months) | Good, 96% | Intention-to-treat analysis. | Double-masked | Groups compared by analysis of covariance. Non-parametric tests also used. |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Comments | External validity |
|---|---|---|
| ***Studies of*** | | |
| Artru 1976[88] (Fair) | More acute subdural hematomas developed and required surgery in the HBOT group. Because of highly stratified groups, sample sizes very small for some analyses. | 60/185 (32%) screened were enrolled "not particularly selected, inclusion depended on availability of chamber." |
| Rockswold 1985,[89] 1992,[90] 1994[91] (Fair) | Not ITT based on exclusion of two patients lost to followup in control group, but was ITT for HBOT group. HBOT group received closer monitoring of ICPs. | Severity of head injury was moderate, with mean GCS 6.2. Selection of subjects is unclear, 168 of 272 (62%) potential subjects included. |
| ***Studies of other types of brain injury*** | | |
| Jianhua 1995[106] (Poor) | | Poor. Not enough details, difference in terminology. Viral cerebritis, age 1-11. No information on selection of patients. |
| ***Studies of*** | | |
| Collet 2001[119] (Fair) | | Children with asthma, seizures or recent otitis media, surgery, botulinum toxin or rhizotomy excluded. Medications stopped 6 weeks prior to trial. |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Randomization/ allocation concealment | Baseline comparability | Timing of baseline measures sufficiently close to intervention | Intervention the same for all patients within groups? | Outcome measures stated and objective? |
|---|---|---|---|---|---|
| Packard 2000[118] (Poor) | Randomization, allocation methods not reported. | Not reported beyond subjects "matched roughly to age and severity." | Yes | Yes | Yes |
| ***Studies of stroke*** | | | | | |
| Anderson 1991[127] (Fair) | Randomization, allocation methods not reported. | Small difference in age, other factors similar, including baseline neurologic scores. | Yes | Yes | Yes (graded neurological exam) |
| Marroni 1987[129] (Poor) | Not randomized (assigned by "first come first to get the free position"). | Not reported. | Not stated | Yes | Yes (Kurtzke scale and author's scale) |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Timing of follow-up measurements stated and adequte? | Followup adequacy (loss to followup) | Handling of dropouts or missing data | Masking | Statistical analysis |
|---|---|---|---|---|---|
| Packard 2000[118] (Poor) | Yes | 3/26 did not complete treatment (12%). Assessment data for both time points available for 20/26 patients (77%). | Results not reported for 3 patients who did not complete treatment. | Physical therapists who completed Peabody Motor Scales, child psychologists who completed Bayley II and Preschool Language Scale tests were masked. Parents were not. | P-values given for mean change scores, analysis not described. |
| ***Studies of stroke*** | | | | | |
| Anderson 1991[127] (Fair) | Yes | Fair- 25/39 (64%) randomized followed for one year, 70% at 4 months. | Not included in analysis, reasons for dropouts reported. | Double-masked | Paired t-tests on difference between exam score at onset and at 4 months. |
| Marroni 1987[129] (Poor) | Yes | Dropouts not reported. | Dropouts not reported. | Single masked (examiner) | Plotted mean improvement in disability index. P-values reported for some measures, no details given. |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Comments | External validity |
|---|---|---|
| Packard 2000[118] (Poor) | Enrolled children of different ages and disabilities, excluded patients with seizures in last 6 months. No information on screening process. | Not enough information to assess. |



***Studies of stroke***

| | | |
|---|---|---|
| Anderson 1991[127] (Fair) | Subjects in the control group had a mean age of 69.1 years, in HBOT group was 63.7 years. Randomization was stratified by baseline neurological exam. Mean number of treatments completed was 10 in control group, 8.9 in HBOT.<br><br>Data analyzed cross-sectionally, rather than as mean change in score for each group. | 39/92 patients screened were enrolled, reasons for exclusion given; only patients with new, moderate, stable deficits included. |
| Marroni 1987[129] (Poor) | | No information on selection, all were no longer undergoing any form of therapy or rehabilitation. |

HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Randomization/ allocation concealment | Baseline comparability | Timing of baseline measures sufficiently close to intervention | Intervention the same for all patients within groups? | Outcome measures stated and objective? |
|---|---|---|---|---|---|
| Nighoghossian 1995[126] (Poor) | Randomization, allocation methods not reported. | Not clear, Orgogozo scale lower in air group at baseline (not statistically significant). | Not stated | Yes | Yes |
| Sarno JE 1972,[128] Sarno MT 1972[130] (Fair) | Randomization, allocation methods not reported. | Not reported. | No | No | Yes |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Timing of follow-up measurements stated and adequte? | Followup adequacy (loss to followup) | Handling of dropouts or missing data | Masking | Statistical analysis |
|---|---|---|---|---|---|
| Nighoghossian 1995[126] (Poor) | Yes | Poor- 7 of 34 (21%) discontinued (13 control and 14 HBOT completed), 4 because of worsening (3 died), 1 MI, claustrophobia, ischemic damage | Not included in analysis | Patients may have been masked, unclear if assessors masked (says "double-masked" in title, but not described) | T-test of means pre and post therapy and comparison of differences of post scores at 6 months and 1 year. |
| Sarno JE 1972,[128] Sarno MT 1972[130] (Fair) | No, only immediately after HBOT | Dropouts not reported | Dropouts not reported | Double-masked | States data did not warrant a detailed statistical analysis, results of token test and Functional Communication Profile were statistically treated to illustrate and confirm absence of improvement. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 8. Quality assessment of controlled studies (continued)

| Author, year (Quality) | Comments | External validity |
|---|---|---|
| Nighoghossian 1995[126] (Poor) | | Radiologic evidence (CT scan) of recent ischemic stroke, and significant deficit on Orgogozo scale required. Excluded: patients with previous stroke, seizures with stroke, significant improvement within 1 hour of stroke, metabolic encephalopathy, significant pulmonary disease, congestive heart failure or uncontrolled hypertension. |
| Sarno JE 1972,[128] Sarno MT 1972[130] (Fair) | Effects are those during treatment only. Documented stroke, but unclear how/why patients selected for study. | N of 60 was planned, but difficulty due to negative patient attitudes changed it to 32. Some patients refused participation when they learned of the absence of beneficial effects. 14 patients rejected for a variety of contraindications. All were examined for pulmonary tests, eliminated if pulmonary status would interfere with the development of high blood oxygen levels, patients with hearing loss excluded. |



HBOT=hyperbaric oxygen therapy; ICP=intracranial pressure; CP=cerebral palsy; GMFM=Gross Motor Function Measure; ITT=intention-to-treat; GCS=Glasgow Coma Scale; CT=computerized tomography; MI=myocardial infarction

## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| ***Traumatic Brain Injury*** | | | | | |
| Artru 1976[94] (Fair) | Before-after | Yes, except one compressed at 2.2 atm instead of 2.5 because of a bad pulmonary condition. | No | Severity, diagnosis of each patient reported. | Not reported |
| Hayakawa 1971[95] (Fair) | Time-series | Yes for dose, number of treatments varied from 10 to 15 | No | No | No |
| Mogami 1969[96] (Poor) | Before-after | No | No | No | Not reported |
| Ren 2001[99] (Poor) | Retrospective cohort | Similar HBOT treatments (not exactly the same). Control interventions actually used not stated. | No | No | No |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| ***Traumatic Brain Injury*** | | | | | |
| Artru 1976[94] (Fair) | Not reported when or how clinical status measured, other measures taken in close proximity. | CBF, metabolic rates for oxygen, glucose and lactate and CSF parameters measured 2 hours after exit from the chamber, clinical status seemed to be measured immediately after exit. | No for clinical status, yes for other measures. | | Not reported how patients selected, no standard assessment of severity of illness, only 6 patients. |
| Hayakawa 1971[95] (Fair) | Yes | Yes | Yes | | Very small sample from one institution, no info on patient selection. |
| Mogami 1969[96] (Poor) | Not reported, "before treatment". | Yes | Subjective, observation (e.g., increased awareness and responsiveness) | | Not clear, some patients comatose, some requiring ventilation, others with only mild deficits. No information on selection of patients, no description of patients except diagnosis and symptoms. |
| Ren 2001[99] (Poor) | Yes | Yes | Yes | | No information on selection. Uneven numbers in groups, reason not given. Mean GCS = 5.3 a& 5.1, not enough other details to assess. |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Rockswold 2001[97] (Fair) | Time-series | Dose and duration the same, number of treatments varied according to response. | No | Yes- time from injury to treatment, type of brain injury and types of multiple trauma. | Yes |
| Sukoff 1982[98] (Poor) | Before-after | No- frequency changed based on ICP and clinical response. | No | No | No |
| ***Other Brain Injury*** | | | | | |
| Chuba 1997[107] (Poor) | Before-after | No | No- all patients presented with new or increasing neurologic deficits. | Some confounding factors listed (e.g., tumor); not controlled for. | Not reported |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Rockswold 2001[97] (Fair) | Yes | Yes | Yes | | Patients were from one Level I trauma center, number screened not given, excluded patients placed in barbiturate-induced coma. |
| Sukoff 1982[98] (Poor) | Not reported | Yes | Subjective | Vague reporting of results, other than ICP measurements. | Only a series of patients in whom HBOT was effective in reducing ICP and showed improved neurological status. No information on how many other patients treated without improvements. Patients requiring vasopressors or with dilated and fixed pupils excluded. |
| ***Other Brain Injury*** | | | | | |
| Chuba 1997[107] (Poor) | Not clear | Yes | No- symptoms, method not described | Very few outcome measures reported. | Children with radiation-induced necrosis of CNS, mostly in supratentorial location. All patients had increasing neurologic deficits and had failed steroids. |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Imai 1974[108] (Poor) | Before-after | Yes | No- not reported | No | Not reported |
| Mathieu 1987[109] (Poor) | Before-after | Dose the same, but number of treatments varied according to condition | No | No | No |
| ***Studies of Cerebral Palsy*** | | | | | |
| Chavdarov 2002[121] (Poor) | Before-after | Yes | No | Reports data grouped by level of severity. | No |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Imai 1974[108] (Poor) | Not clear | "After one or two treatments" | Yes | Few details about how subjects selected or if/when baseline tests done. | No information on selection of patients, no description of patients except diagnosis; very mixed group selected: patients with presenile dementia, chronic alcoholism, cerebral vascular disease, and CO intoxication. |
| Mathieu 1987[109] (Poor) | Baseline information not reported except for GCS measure on admission, timing not clear in relation to HBOT | Timing not reported | Death, neurological sequelae described, "recovery without sequelae" not defined, not objective. Method of measuring outcomes not reported. | | All patients at one institution with attempted hanging, 71 (42%) had psychiatric illness. |
| ***Studies of Cerebral Palsy*** | | | | | |
| Chavdarov 2002[121] (Poor) | Yes | Yes | Yes, but measured by the same assessor before and after treatment | | Not clear how patients selected, all were from one hospital in Bulgaria, described inclusion criteria (history of seizures excluded, among other). |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Machado 1989[122] (Poor) | Time-series | No | No | No | No |
| Montgomery 1999[123] (Fair) | Before-after | No, varied by center | Yes. Inclusion criteria stated functional plateau in rehabilitation for 12 months (defined as no measurable functional changes in gross motor performance as documented by their physical therapists. | Potential effect of age is addressed by type of test given. | Not clear: outcome assessors had "no contact" with children during HBOT; but not necessarily masked. |
| ***Studies of Stroke*** | | | | | |
| Hart 1973[149] (Poor) | Time-series | No, same pressure and time, but different drug therapies and a second course given if improvement seen | No- criteria were 3 weeks stable and at least 4 weeks from onset of ischemic attack. | No- all patients received physical therapy, gait training, and speech therapy. Only age and other medications given in different recovery groups were reported, but not controlled for. | No |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Machado 198122 (Poor) | Not clear ("had been reviewed before and after therapy") | Yes | Subjective-observations | Few details about intervention, or outcome measurements | Retrospective review of CP patients treated at one institution, states that report is observations based on clinical findings and without scientific documentation, followed up only 39% (only those that lived in Sao Paolo). Diagnosis not defined. |
| Montgomery 1999[123] (Fair) | Pre and post evaluations separated by 37.2 +/- 8 days | Pre and post evaluations separated by 37.2 +/- 8 days | Stated, some subjective, some objective | This study randomized subjects to two weeks of HBOT or 4 weeks of HBOT, with no control group. | Excluded were those with recent rhizotomy, thoracic surgery, epilepsy, cancer, asthma, VP shunts, previous HBOT, anti-spasticity meds, or behavior problems. |
| ***Studies of Stroke*** | | | | | |
| Hart 1973[149] (Poor) | Not reported | Not clear (period of 7 days reported for improved patients, but duration of follow-up not clear). | Stated, but not clearly objective (neurologic exam, EEG, radioisotope scans) | | Defined as middle cerebral artery ischemia (proven by angiography or radioisotope scan), neurologic state stable for at least 3 weeks, and at least 4 weeks from onset. No information on patient selection. |

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## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Holbach 1977a[141] (Poor) | Time-series | Yes, except TIA patients had only 1 treatment ("test treatment"), but results are reported separately. | No States 38 patients had complete stroke, 36 were chronic stroke patients, but timing of HBOT since onset of stroke not reported. | No | Not reported |
| Holbach 1977b[142] (Poor) | Time-series | Yes for dose, number of treatments varied from 10 to 15. | No | Patients selected for surgery based on initial response to HBOT. | Not reported |
| Imai 1974[108] (Poor) | Before-after | Yes | No- not reported. | No | Not reported |
| Jain 1989[134] (Poor) | Before-after | Yes | No- time since onset ranged from 3 months to 5 years, all were undergoing stroke rehabilitation. | No, all patients had simultaneous physical therapy. | No |

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## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Holbach 1977a[141] (Poor) | "Before HBOT treatment" | "During and at conclusion of HBOT" sessions | States neurological exam, but not described | Outcome measurements unclear. | Diagnosis vague, no information on patient selection. |
| Holbach 1977b[142] (Poor) | Yes | Yes | Neurological exam and neurological deficits, not specified | | All patients were judged suitable to undergo surgery if necessary, no other information on patient selection. |
| Imai 1974[108] (Poor) | Not clear | "After one or two treatments" | Yes | Few details about how subjects selected or if/when baseline tests done. | No information on patient selection, no description except diagnosis; mixed group selected: patients with presenile dementia, chronic alcoholism, cerebral vascular disease & CO intoxication. |
| Jain 1989[134] (Poor) | Yes | Yes | Yes | Results on spasticity are very difficult to interpret (stratification of results not explained), also subjects continued to receive PT after HBOT during followup. | 21/50 patients already undergoing rehabilitation with PT in HBOT chamber, only those with clinically assessable spasticity are included. Diagnosis vague. |

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## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Jain 1990[143] (Poor) | Time-series | Yes | No One patient was 5 years post-stroke, all others less than 12 months (range 3 weeks-11 months); no day-to-day neurological changes during first week of admission to clinic. | No, all patients had simultaneous physical therapy. | Not reported |
| Kapp 1981[144] (Poor) | Time-series | Yes. | No- HBOT started on day of diagnosis or after obtaining consent from family. | Yes, stratified results but no attempt to control statistically. | Not reported |

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## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Jain 1990[143] (Poor) | Yes | Yes | Yes | Only patients seen by senior authors included, only 10 of 25 had spasticity measurements recorded. Data for grip strength in table not discernable (e.g. before = 0/32 and after = 8). A footnote refers to stronger/weaker hand strength. First 8 patients recevied PT immediately after HBOT, and noticed that this significantly helped with spasticity, so the rest received PT during HBOT treatments. | Almost no description of patients given, except that they had occlusive cerebrovascular disease, 24 had hemiplegia. Spasticity grade at baseline ranged from 2-5 (scale 0-5), mean 3.4 (only 10 patients with this data). |
| Kapp 1981[144] (Poor) | Yes | Yes | Some measures objective and some subjective | Purpose of study was to use HBOT to identify subjects who are candidates for revascularization | Inclusion criteria described, all patients seen by author in 2-year period who fit criteria enrolled, number screened and eligible not given. |

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## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Li 1998[135] (Poor) | Before-after | Dose and duration the same, but course of 15 treatments varied from 3-4, and "rarely" more. | No- some patients were 3 years post-stroke but results are not reported separately by time since stroke. Range was < 1 month to over 3 years. | No. | Not reported |
| Neubauer 1980[139] (Poor) | Before-after | No. | Yes for some patients (time of HBOT treatment from onset ranged from 4 hours to 10 years). | No- patients received simultaneous physical therapy "when indicated". Severity reported, no statistical tests done. Results reported by timing of treatment from onset of stroke. | No |
| Noguchi 1983[136] (Poor) | Before-after | No. Number of treatments per day and total varied based on condition of patient. Varied from one time to 60 times, average of 17.2 per case. | No. | No. | Not reported |

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## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Li 1998[135] (Poor) | Not reported | Not reported | Stated, not objective (assessment of clinical symptoms by neurologists) | Too few details to assess. A subset was compared to "controls" - no details on how either gorup selected | No information on selection of patients, limited description of patients. |
| Neubauer 1980[139] (Poor) | Not reported | Not reported | Subjective | | Some information on patients given, no info on selection process. Because consecutive patients, may be good but baseline characteristics not reported. |
| Noguchi 1983[136] (Poor) | Not reported | Not reported | No, clinical assessment, signs and symptoms, physical exam, not described. | | No information on patient selection, diagnosis vague |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Pilotti 1991[147] (Poor) | Retrospective comparison of cohorts | Similar HBOT treatments (not exactly the same). Control interventions actually used not stated. | NA | Patients in control and treatment groups were treated at 2 different institutions. Small differences with respect to age, sex, clinical history. Respiratory insufficiency, vascular insufficiency of inferior limbs and arterial hypertension were higher in HBOT-treated group ($p < 0.05$). | Yes |
| Saltzman 1965[145] (Poor) | Time-series | No In 18 patients, HBOT given within 7 hours of onset of symptoms, in 7 patients, given 7-30 days after onset. Myringotomies performed before in "most" patients. Initial studies used 3.04 atm for < 1 hour, in later treatments, pressure below 2.5 ata, permitting "prolonged" exposure. | No- patients had treatment <7 hours to 30 days after onset of stroke. | Describe separately patients who received HBOT soon after onset, but other factors not addressed | No |
| Steenblock 1998[137] (Poor) | Before-after | No. Treatment plans and physical therapy adjusted as the patient's condition warranted. | Yes for some patients (time of HBOT treatment from onset ranged from 1 month to 10 years, average 29 months). | No- all patients received physical therapy, electrical stimulation, hot or cold packs, ultrasound, short wave diathermy, paraffin bath therapy, and biofeedback. | No |

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## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Pilotti 1991[147] (Poor) | Yes | NA (retrospective cohort) | No dropouts or missing data reported | Overall mortality rates at the 2 hospitals are not given for comparison. | No information on patient selection |
| Saltzman 1965[145] (Poor) | Not reported | Unclear. One patient reported out to 10 days, others only immediately after HBOT. | Subjective (observation) | Very vague description of improvements seen during and shortly after HBOT. | No information on selection of patients, no description of patients except diagnosis. Diagnosis vague |
| Steenblock 1998[137] (Poor) | Evaluation at the "beginning of the program and at the end" | "At the end" | Stated, subjective | Results are presented as % improvement or improvement no/yes. | No information on selection of patients, reports that 100% of patients improved on one or more functions, little description of patients. Baseline severity of disability not presented. |

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## Evidence Table 9. Quality assessment of observational studies (continued)

| Author year (Quality) | Study design | Exposure measurement (HBOT therapy same for all participants?) | Stable baseline established? | Confounding factors addressed? (severity of disease, other treatment); control for confounders? | Masking (patients, outcome assessors) |
|---|---|---|---|---|---|
| Tsuro[138] 1983 (Poor) | Before-after | Dose the same, but number of treatments varied. | No. | No. | No |
| Wassman 1986[146] (Poor) | Time-series | Yes for dose, number of treatments varied from 10 to 15. | No- patients were about 3 months post-stroke. | No. | Not reported |
| Zhou Shn-rong 1995[110] (Poor) | Before-after | No, dose the same but number of treatments varied. | No- HBOT given 2-3 days after stroke. | No. | No |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

## Evidence Table 9. Quality assessment of observational studies

| Author year (Quality) | Timing of baseline measures stated and sufficiently close to intervention? | Timing of followup measurements stated and adequte? | Outcome measures stated and objective? | Comments | External validity |
|---|---|---|---|---|---|
| Tsuro[138] 1983 (Poor) | Not reported | Not reported | Observations, not objective, not stated how determined | | Series of cases treated with HBOT at one institution, no information on selection of patients for treatment. Only 79 cases of "over a hundred" treated are presented. |
| Wassman 1986[146] (Poor) | Yes | Yes | "Motor deficit" method of measurement not described. | | Only includes patients who showed a definite increase of electrical power equivalent on EEG after an HBOT series. |
| Zhou Shn-rong 1995[110] (Poor) | Not reported | Not reported | Yes, but not objective | Few details about how subjects selected or if/when baseline tests done. | No info on selection of patients, no way to compare patients, e.g. described as 'deep coma' |

HBOT=hyperbaric oxygen therapy; atm=atmospheres; ICP=intracranial pressure; TIA=transient ischemic attack; CBF=cerebral blood flow; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; CO=carbon monoxide; CP=cerebral palsy; PT=physical therapy; EEG=electroencephalogram; CNS=central nervous system

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# Appendix A. Indications for HBOT

| Food and Drug Administration | | Undersea and Hyperbaric Medical Society | Centers for Medicare and Medicaid Services |
|---|---|---|---|
| 1. | Air or gas embolism | Air or gas embolism | Gas embolism, (ICD-9-CM diagnosis 958.0, 999.1). |
| 2. | Carbon monoxide poisoning and smoke inhalation | Carbon monoxide poisoning | Acute carbon monoxide intoxication, (ICD-9-CM diagnosis 986) . |
| 3. | Carbon monoxide poisoning complicated by cyanide poisoning | Carbon monoxide poisoning complicated by cyanide poisoning | Cyanide poisoning (ICD-9-CM diagnosis 987.7, 989.0). |
| 4. | Clostridial myonecrosis | Gas gangrene | Gas gangrene, (ICD-9-CM diagnosis 0400). |
| 5. | Crush injury | Crush injury | Crush injuries and suturing of severed limbs. (ICD-9-CM diagnosis 927.00-927.03, 927.09-927.11, 927.20-927.21, 927.8-927.9, 928.00- 928.01, 928.10-928.11, 928.20-928.21, 928.3, 928.8-928.9, 929.0, 929.9, 996.90-996.99.) |
| 6. | Compartment syndrome, acute traumatic ischemias | Compartment syndrome and other acute traumatic ischemias | Acute traumatic peripheral ischemia. (ICD-9-CM diagnosis 902.53, 903.1, 903.01 904.0, 904.41.) |
| 7. | | | Acute peripheral arterial insufficiency, (ICD-9-CM diagnosis 444.21, 444.22, 444.81). |
| 8. | Decompression sickness | Decompression sickness | Decompression illness, (ICD-9-CM diagnosis 993.2, 993.3). |
| 9. | Enhancement of healing in selected problem wounds | Enhancement of healing in selected problem wounds | |
| 10. | Exceptional blood loss | Exceptional blood loss (anemia) | |
| 11. | Necrotizing soft tissue infections | Necrotizing soft tissue infections | Progressive necrotizing infections (necrotizing fasciitis), (ICD-9-CM diagnosis 7278.86). |
| 12. | Osteomyelitis (refractory) | Refractory osteomyelitis | Chronic refractory osteomyelitis (ICD-9-CM diagnosis 730.10-730.19). |
| 13. | Radiation tissue damage | Delayed radiation injury (soft tissue and bony necrosis) | Osteoradionecrosis (ICD-9-CM diagnosis 526.89). |

| Food and Drug Administration | | Undersea and Hyperbaric Medical Society | Centers for Medicare and Medicaid Services |
|---|---|---|---|
| 14. | | | Soft tissue radionecrosis (ICD-9-CM diagnosis 990). |
| 15. | Skin grafts & flaps (compromised) | Skin grafts & flaps (compromised) | Treatment of compromised skin grafts, (ICD-9-CM diagnosis 996.52; excludes artificial skin). |
| 16. | Thermal burns | Thermal burns | |
| 17. | Adjunctive hyperbaric oxygen in intracranial abscess | Intracranial abscess | |
| 18. | | Actinomycosis | Actinomycosis(ICD-9-CM diagnosis 039.0-039.4, 039.8, 039.9). |

# Appendix B. Research Team, Technical Expert Advisory Group, and Peer Reviewers

## Research Team:

Marian S. McDonagh, PharmD, Principal Investigator
Assistant Professor of Medical Informatics & Clinical Epidemiology
Oregon Health & Science University
Portland, Oregon
Previously: Senior Research Associate
Center for Health Research
Kaiser Permanente Northwest
Portland, Oregon

Mark Helfand, MD, MS
Director, Evidence-based Practice Center
Associate Professor of Medicine
and Medical Informatics & Clinical Epidemiology
Oregon Health & Science University
Portland, Oregon

Joan S. Ash, MLS, MBA, PhD
Associate Professor of Medical Informatics & Clinical Epdemiology
Oregon Health & Science University
Portland, Oregon

Barry S. Russman, MD
Professor of Pediatrics and Neurology
Oregon Health & Science University
Portland, Oregon

P. Zoë Stavri, PhD
Assistant Professor of Medical Informatics & Clinical Epidemilogy
Oregon Health & Science University
Portland, Oregon

Kathryn Pyle Krages, AMLS, MA
Administrator, OHSU Evidence-based Practice Center
Division of Medical Informatics & Clinical Epidemiology
Oregon Health & Science University
Portland, Oregon

Susan Carson, MPH
Senior Research Associate
Division of Medical Informatics & Clinical Epidemilogy
Oregon Health & Science University
Portland, Oregon

Daphne Plaut, MLS
Research Center Librarian
Center for Health Research
Kaiser Permanente Northwest
Portland, Oregon

Martha Swain
Senior Technical Writer-Editor
Center for Health Research
Kaiser Permanente Northwest
Portland, Oregon

Debra Burch
Secretary
Center for Health Research
Kaiser Permanente Northwest
Portland, Oregon

Susan Wingenfeld
Research Assistant
Division of Medical Informatics & Clinical Epidemiology
Oregon Health & Science University
Portland, Oregon

## Technical Expert Advisory Group:

Mary Barnease
New Orleans, Louisiana

Randall M. Chesnut, MD
Associate Professor of Neurosurgery
Oregon Health & Science University
Portland, Oregon

Dr Jean-Paul Collet
Randomised Clinical Trial Unit
SMBD Jewish General Hospital
Montreal, Quebec, Canada

Paul G. Harch, MD
Clinical Assistant Professor
Director of Hyperbaric Medicine Fellowship
President, International Hyperbaric Medical Association
Department of Medicine, Section of Emergency and Hyperbaric Medicine
Louisiana State University School of Medicine
New Orleans, Louisiana

Jeffrey Shuren, MD, JD
Centers for Medicare and Medicaid Services
Coverage and Analysis Group
Baltimore, Maryland

Roger P. Simon, MD
Robert Stone Dow Chair of Neurology
Director, Dow Neurobiology Laboratories
Legacy Health System
Portland, Oregon

William A. Spisak, MD
Internal Medicine
Providence Health System
Portland, OR

Tom Workman MS, CHT
Director, Quality Assurance & Regulatory Affairs
Undersea & Hyperbaric Medical Society
San Antonio, Texas

## Peer Reviewers:

David C. Anderson, MD
Professor of Neurology
University of Minnesota
Minneapolis, Minnesota

Stephen Ashwall, MD
Representing the Child Neurology Society
Loma Linda University Children's Hospital
Loma Linda, California

David Atkins, MD, MPH
Chief Medical Officer, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality
Rockville, Maryland

Harvey Bernard, MD
Medical Director
Office of Medicaid Management
Albany, New York

Ronald Deicas, MD
Center for Medicare and Medicaid Services
Baltimore, Maryland

Bruce Flareau, MD
Representing American Academy of Family Physicians
Mease Hospital
Clearwater, Florida

George Gaebler, MSEd, RRT, FAARC
Representing American Academy of Respiratory Therapists
Syracuse, NY

Murray Goldstein, DO
United Cerebral Palsy
Research and Education Foundation
Washington, DC

Neil B. Hampson, MD
Representing Undersea and Hyperbaric Medical Society
Section Head, Pulmonary and Critical Care Medicine
Medical Director, Hyperbaric Department
Virginia Mason Medical Center
Seattle, WA

Paul G. Harch, MD
Clinical Assistant Professor
Director of Hyperbaric Medicine Fellowship
President, International Hyperbaric Medical Association
Department of Medicine, Section of Emergency and Hyperbaric Medicine
Louisiana State University School of Medicine
New Orleans, Louisiana

George Hart, MD
Long Beach Memorial Hospital
Long Beach, CA

Bonnie Kaplan, PhD
Yale Center for Medical Informatics
New Haven, Connecticut

Edgar Kenton III, MD
Representing American Heart Association
Wynnewood, Pennsylvania

Valerie Larsson-Lohr
Representing Baromedical Nurses Association
San Antonio, TX

David Montgomery, MD
Co-chair, Seagram Science Sports Centre
Faculty of Education
McGill University
Montreal, Quebec, Canada

Richard Neubauer, MD
Ocean Hyperbaric Center
Lauderdale-by-the-Sea, Florida

Nancy Pearson, PhD
National Center for Complementary and Alternative Medicine
Bethesda, Maryland

Roger P. Simon, MD
Robert Stone Dow Chair of Neurology
Director, Dow Neurobiology Laboratories
Legacy Health System
Portland, Oregon

Ann Tilton, MD
Representing American Academy of Pediatrics
Children's Hospital
New Orleans, Louisiana

Elmer Villanueva, MD, ScM
Centre for Clinical Effectiveness
Monash Medical Centre
Clayton, Australia

Tom Workman MS, CHT
Director, Quality Assurance & Regulatory Affairs
Undersea & Hyperbaric Medical Society
San Antonio, Texas

# Appendix C. Literature Search Strategies

## Summary of Online Searching

Stroke or Brain Injury Search Terms

MeSH Terms
Explode brain diseases
Explode confusion
Explode meningitis
Explode coma
Explode craniocerebral trauma

Textwords
Stroke
TIA
Transient ischemi$
Transient ischaemi$
Brain
Cerebro$
Cerebral$
Intracranial$
Concussion$
Confusion$
Coma$
Stupor$
Encephalopath$
Meningitis
Encephalitis
Dementia
Leukoencephalopath$
Leukodystroph$
Cortical dysplas$
Craniocerebral$

Hyperbaric Oxygen Therapy Search Terms

MeSH Terms
Hyperbaric oxygenation

Textwords
Hyperbaric oxygen$
Hyperbaric therap$

## Search Strategy

[sh] = subject heading, [ti] = title word, [ab] = word in abstract

1 exp Brain Diseases/ [sh]
2 exp CONFUSION/ [sh]
3 exp MENINGITIS/ [sh]
4 exp COMA/ [sh]
5 exp Craniocerebral Trauma/ [sh] or exp Head Injury/ [sh]
6 (stroke or tia or brain or cerebro$ or cerebral$) [ti,ab,sh]
7 (transient ischemi$ or transient ischaemi$) [ti,ab,sh]
8 (intracranial$ or concussion$ or confusion$ or coma$) [ti,ab,sh]
9 (stupor$ or encephalopath$ or meningitis) [ti,ab,sh]
10 (encephalitis or dementia or leukoencephalopath$) [ti,ab,sh]
11 (leukodystroph$ or craniocerebral$) [ti,ab,sh]
12 cortical dysplas$ [ti,ab,sh]
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 Hyperbaric Oxygenation/ [sh]
15 hyperbaric oxygen$ [ti,ab,sh]
16 hyperbaric therap$ [ti,ab,sh]
17 14 or 15 or 16
18 13 and 17
19 limit 18 to (human and english language)

### Databases & Results

| Database | Date of search | Time period covered | Search interface | Citations | Comments |
|---|---|---|---|---|---|
| **MEDLINE & PreMEDLINE** | 3/23/01 | 1966- | OVID | 400 | |
| **HealthStar** | 3/23/01 | 1975-2000 | OVID | 2 | Excluding MEDLINE citations |
| **CINAHL** | 3/23/01 | 1982- | OVID | 17 | |
| **Cochrane Database of Systematic Reviews** | 3/23/01 | Issue 1 2001 | Update Software CD | 2 | |
| **Cochrane Controlled Trials Register** | 3/23/01 | Issue 1 2001 | Update Software CD | 16 | Excluding MEDLINE citations |
| **DARE** | 3/23/01 | Issue 1 2001 | Update Software CD | 1 | |
| **AltHealthWatch** | 3/23/01 | 1990- | EBSCOhost | 4 | |
| **MANTIS** | 3/23/01 | 1880- | OVID | 1 | |
| **EMBASE** | 3/27/01 | 1980- | OVID | 269 | Much overlap with MEDLINE |

## Update Searches and Results

| Database | Date of search | Time period covered | Search interface | New Citations | Comments |
|---|---|---|---|---|---|
| **MEDLINE & PreMEDLINE** | 1/30/02 | April 2001 - | OVID | 46 | |
| | 7/31/03 | February 2002 - | OVID | 10 | |
| **HealthStar** | | | | | Defunct database |
| **CINAHL** | 1/30/02 | April 2001 - | OVID | 2 | |
| | 7/31/03 | February 2002 - | OVID | 0 | |
| **Cochrane Database of Systematic Reviews** | 2/6/02 | Issue 1 2002 | OVID | 5 | |
| **Cochrane Controlled Trials Register** | 2/6/02 | Issue 1 202 | OVID | 29 | Excluding MEDLINE citations |
| **DARE** | 2/6/02 | Issue 1 2002 | OVID | 1 | |
| **AltHealthWatch** | 2/12/02 | April 2001 - | EBSCOhost | 3 | |
| **MANTIS** | 2/12/02 | April 2001 - | OVID | 2 | |
| **EMBASE** | 2/11/02 | April 2001 - | OVID | 34 | Much overlap with MEDLINE |
| | 7/31/03 | February 2002 - | OVID | 6 | Overlap with MEDLINE |
| **Health Technology Assessment (HTA)** | 2/12/02 | | University of York website | 6 | |
| **Undersea & Hyperbaric Medical Society Database** | 2/26/02 | | UHMS proprietary system | 416 | Much overlap with MEDLINE |

A small amount of overlap between the databases, including overlap with the previous search, was apparent in the Cochrane Controlled Trials Register, EMBASE, and the Undersea & Hyperbaric Medical Society Database. After eliminating these duplicate citations and conducting dual abstract assessment, 110 full papers were ordered. Eighty-seven of these were

from the Undersea & Hyperbaric Medical Society Database, which did not provide abstracts for titles and included a large number of meeting abstracts. In addition to these, one member of the Technical Expert Advisory Group provided articles and meeting abstracts from his personal library (Dr. Paul Harch).

# Appendix D. Quality Assessment Criteria

## US Preventive Services Task Force Criteria for Grading the Internal Validity of Individual Studies

(Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prev Med. 2001;20(3S):21-35.)

### Randomized Controlled Trials and Cohort Studies

Seven categories of criteria apply to RCTs and cohort studies. They include:

1. Initial assembly of comparable groups.
   a. For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
   b. For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
2. Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
3. Levels of follow-up: differential loss between groups; overall loss to follow-up.
4. Measurements: equal, reliable, and valid, and including masking of outcome assessment.
5. Clear definition of interventions.
6. All important outcomes considered.
7. Analysis:
   a. For RCTs: intention-to-treat analysis.
   b. For cohort studies: adjustment for potential confounders.

The definitions of the three rating categories for these types of studies are as follows:

**Good**: Comparable groups assembled initially and maintained throughout the study; follow-up at least 80 percent; reliable and valid measurement instruments applied equally to the groups; outcome assessment masked; interventions defined clearly; all important outcomes considered; appropriate attention to confounders in analysis; for RCTs, intention-to-treat analysis.

**Fair**: Generally comparable groups assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments acceptable (although not the best) and generally applied equally; outcome assessment masked; some, but not all important, outcomes considered; appropriate attention to some, but not all, potential confounders; for RCTs, intention-to-treat analysis.

**Poor**: Groups assembled initially not close to being comparable or not maintained throughout the study; measurement instruments unreliable or invalid or not applied at all equally among groups; outcome assessment not masked; key confounders given little or no attention; for RCTs, no intention-to-treat analysis.

## Criteria for Grading the Overall Evidence

### Aggregate Internal Validity

This category refers to the overall extent to which data are valid for conditions addressed within studies. It would be rated according to quality grading information about individual studies.

### Aggregate External Validity

This category concerns the generalizability of evidence to questions addressed by the linkage. This would include the concordance between populations, interventions, and outcomes in the studies reviewed (on the one hand) and those to which the linkage pertains (on the other). In short, this category reflects the applicability of the evidence to real-world conditions.

The Methods Work Group expects that differences between conditions examined in studies and those addressed by the linkages should be considered if they could potentially influence outcomes. These might include (but not necessarily be limited to): (a) biologic or pathologic characteristics; (b) incidence and prevalence of clinical conditions; (c) distribution of comorbid conditions that might affect outcomes; and (d) likelihood of acceptability and adherence on the part of patients or providers (or both).

### Consistency

This category relates to the overall "coherence" of the body of evidence relating to the linkage. Specifically, it includes the number of studies, the homogeneity of those studies (in terms of clinical conditions, populations, settings, and the like), the level of precision of findings in the studies, and the direction of results. In addition, it can include dose-response relationships.

# NHS Centre for Reviews and Dissemination, based at University of York

(Available at http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

### Experimental Studies

1. Was the assignment to the treatment groups really random?
   Adequate approaches to sequence generation
   - Computer-generated random numbers
   - Random numbers tables

   Inadequate approaches to sequence generation
   - Use of alternation, case record numbers, birth dates or week days
2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization
   - Centralized or pharmacy-controlled randomization

- Serially-numbered identical containers
- On-site computer based system with a randomization sequence that is not readable until allocation
- Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients

Inadequate approaches to concealment of randomization

- Use of alternation, case record numbers, birth dates, or week days
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were the outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include and intention-to-treat analysis?

## Observational Studies

Cohort studies:

- Is there sufficient description of the groups and the distribution of prognostic factors?
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all important confounding factors?
- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose-response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was followup long enough for the outcomes to occur?
- What proportion of the cohort was followed up?
- Were dropout rates and the reasons for dropout similar across intervention and unexposed groups?

Case series:

- Is the study based on a representative sample selected from a relevant population?
- Are the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was followup long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of sub series are being made, was there sufficient description of the series and the distribution of prognostic factors?

# Appendix E. Excluded Studies


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# Appendix G. Unretrieved Studies


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# Appendix H. Outcome measures used in HBOT studies[1;2]

| Test Name | Description | Strength of Test | Weakness of Test |
|---|---|---|---|
| 2-Point Discrimination Test | With eyes closed, pt asked whether he feels 1 or 2 pins touching tip of finger | Part of Neurological exam; a test of parietal lobe function (sensory part of the brain) | Not very sensitive and not very specific |
| Ashworth Scale (Spasticity) | Amount of resistance that examiner feels when passively moving a joint | Inexpensive; no equipment needed; a test of muscle tone | Unreliably unless examiner very well trained; inter-rater reliability is generally poor; not specific for spasticity |
| Bender-Gestalt Test | Pt asked to reproduce figures; a written test | Inexpensive; can be given in 10 minutes; a test of visual-perception | Assumes that pt had normal visual-perception prior to the injury |
| CT Scan White Matter Low Attenuation Volume | Area of decreased blood flow in the Scan in the white matter part of the brain | High correlation with poor blood flow in the brain | Requires availability of equipment; about $500 per test |
| Digit Span | Part of the WAIS-R; ask pt to repeat digits as presented by examiner; a test of attention | Reliable; validated and easily administered | Not sensitive |
| Disability Rating Scale | Sum of ratings over different scales of disability and impairment | Validated, excellent reliability and administered in 5 minutes | Not helpful for mild to moderate TBI |
| Double Simultaneous Stimulation Test | Same as 2-point discrimination | | |
| Electroencephalogram (EEG) | Recording the electrical activity of the brain | Easily performed; excellent reliability | Not specific for a disability |
| Functional Independent Measure (FIM) | Measures the degree of assistance a pt requires following recovery from a TBI | 30 minute or less to administer; reliable | Cognitive, and behavioral aspects of test not adequate to evaluate TBI pts |
| Glasgow Coma Scale (GCS) | A scale that semi-objectifies the level of coma (3-15) | Administered at the bed-side; used for assessment of a pt in coma | Must use with other evaluations before offering a prognosis of recovery from the TBI |
| Glasgow Outcome scale (GOS) | Ordinal rating of Global Outcome (1-5) | Good reliability; administrated at bedside; correlates with GCS | Not very sensitive |
| Gross Motor Function Measure (GMFM) | Developed to measure changes in motor function in children with CP | Validated, reliable and sensitive | Limited to Children less than age 7 years |
| Mental Status Examination | Part of Routine Neurological Examination; a screening test for memory, general knowledge, attention, etc. | Easily administered; reliable and valid | A Screening test; not sensitive and not specific. |

## Outcome measures used in HBOT studies (continued)

| Test Name | Description | Strength of Test | Weakness of Test |
|---|---|---|---|
| Motor power of hand by dynamometer | Hand held gauge to determine strength of hand grasp | Reliable and easily administered | Very specific for strength; not correlated with function |
| Multiple Modality Evoked responses | Tests of pathway for vision, hearing and sensation | Easily administered, reliable | Non-specific |
| Repetitive Thumb/finger Movements | Ask pt to rapidly oppose finger and thumb; standardized part of the neurologic exam; test of coordination of fine motor movements | Easily administered | Non-specific; very subjective |
| SPECT (Single Photon Emission Computed Tomography) | Single proton emission computed tomography (SPECT) measures the uptake and distribution of a radioactive nucleotide within the brain and is believed to be proportional to cerebral blood flow (CBF). The CBF demonstrated by SPECT correlates with the metabolic activity that is shown by proton emission tomography (PET). | Less expensive form of functional imaging than the PET scan. This procedure can detect generalized hypo metabolism secondary to anoxia for example. In severe head trauma there is a strong association between axonal injury and decreased metabolism within the brain | Limited prognostic value for recovery for stroke; clinical significance of abnormal SPECT in TBI unknown. To date, there are no studies correlating a change in CBF asdemonstrated by SPECT and a functional change in the patient. |
| Token Test-test for receptive aphasia | Tokens presented to patient of increasing length and complexity | Educational level does not contaminate the test | |
| Volume of hypodensity on CT Scan | A finding on CT scan that is consistent with an infarction | Well standardized | Not specific; a finding caused by change in blood flow to the brain |
| WAIS-R (Wechsler Adult Intelligence Scale –Revised) | A validated and reliable test of Intelligence | Good predictor of academic intelligence, especially when recovering form a TBI | May be preserved after TBI despite debilitating problems with executive functions or memory |
| Wechsler Memory Scale | Well standardized test of immediate recall and long-term memory | | Insensitive for pts with profound memory deficits |

The following tests were utilized in one or more of the studies cited; references for these tests could not be found.

Guild Memory test
Hunt-Minnesota Test
Jebsen's test (Fine Motor Function )
Memory Drum test
Neurologic Disability Evaluation
Neurology Recovery Score
Orgogozo Scale
Rankin Disability Scale
Reaction Time (visual and auditory)
Rheology studies
Stockton Geriatric Scale
Tien's Organic integrity Test
Trouilla Scale
Wechsler Mental status

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# Abbreviations and Acronyms

**ATA** = Atmospheres absolute

**ATM** = Atmosphere

**BI** = Brain injury

**CDER** = Center for Drug Evaluation and Research

**CDRH** = Center for Devices and Radiological Health

**CINAHL** = Cumulative Index to Nursing & Allied Health

**CNS** = Central nervous system

**CP** = Cerebral palsy

**CT** = Computerized tomography

**DARE** = Database of Abstracts of Reviews of Effectiveness

**EEG** = Electroencephalogram

**EIAB** = Extra-intracranial arterial bypass

**FIM** = Functional Independence Measure

**GCS** = Glasgow Coma Scale

**GMFM** = Gross Motor Function Measure

**GOS** = Glasgow Outcomes Scale

**HBOT** = Hyperbaric oxygen therapy

**HealthSTAR** = Health Service Technology, Administration and Research

**ICP** = Intracranial pressure

**ICU** = Intensive Care Unit

**IND** = Investigational New Drug Application

**IRB** = Institutional Review Board

**JCAHO** = Joint Commission on Accreditation of Healthcare Organizations

**LOS** = Length of stay

**MANTIS** = Manual, Alternative and Natural Therapy

**MRI** = Magnetic resonance imaging

**NRCT** = Nonrandomized controlled trial

**NS** = Nonsignificant

**PEDI** = Pediatric Evaluation of Disabilities Inventory

**RCT** = Randomized controlled trial

**SPECT** = Single Photon Emission Computed Tomography

**TBI** = Traumatic brain injury

**TEAG** = Technical Expert Advisory Group

**TIA** = Transient ischemic attack

# Glossary of Terms

**Abstraction:** The method by which reviewers or researchers read scientific articles and then collect and record data from them.

**Adverse effect:** A harmful, unintended reaction to a diagnostic or therapeutic intervention.

**Allocation concealment:** The process used to prevent knowledge of group assignment in a randomized controlled trial before the actual intervention/treatment/exposure is administered.

**Atmospheres (atm):** Term commonly used for atmospheres absolute (see following term).

**Atmospheres absolute (ata):** Units of pressure; 1 atmosphere is pressure of the atmosphere at sea level.

**Barotrauma:** Physical injury sustained as a result of exposure to increased environmental air pressure; a condition of discomfort in the ear caused by pressure differences between the inside and the outside of the eardrum.

**Before-after study:** An observational study in which an outcome is measured in the same group of patients at one point before and after an intervention.

**Bias:** Any systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of effect.

**Case series:** A report on a series of patients with an outcome of interest. No control group is involved.

**Cohort study:** Involves identification of two groups (cohorts) of patients, one that did receive the exposure of interest, and one that did not, and following these cohorts forward for the outcome of interest.

**Consistency:** For any given topic, the extent to which similar findings are reported using similar or different study designs.

**Controlled study:** See randomized controlled trial, nonrandomized controlled trial.

**Fair-quality study:** A study that meets the following criteria: Generally comparable groups assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for randomized controlled trials. See also good quality study, poor quality study.

**Focus group:** A formal discussion with a group of people on a specific topic. The group is facilitated by a leader who keeps participants focused on the topic of interest. The purpose of a focus group is to collect in-depth information from a group of people who represent the population of interest.

**Glasgow Coma Scale:** A scoring system used in quantifying level of consciousness following traumatic brain injury.

**Glasgow Outcomes Scale:** A scoring system used to predict the level of long-term outcome for patients following a traumatic brain injury.

**Good-quality study:** A study that meets the following criteria: comparable groups are assembled initially and maintained throughout the study; follow-up at least 80 percent; reliable and valid measurement instruments applied equally to the groups; interventions clearly defined; important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for randomized controlled trials, intention-to-treat analysis is used. See also fair quality study, poor quality study.

**Gray literature:** foreign or domestic open source material that usually is available through specialized channels and may not enter normal channels or systems of publication, distribution, bibliographic control, or acquisition by booksellers or subscription agents (Interagency Gray Literature Working Group, "Gray Information Functional Plan," 18 January 1995).

**Hyperbaric oxygen therapy (HBOT):** The inhalation of 100 percent oxygen inside a hyperbaric chamber that is pressurized to greater than one atmosphere.

**Increased intracranial pressure (ICP):** A condition in which the pressure of the cerebrospinal fluid or brain matter within the skull exceeds the upper limits for normal pressure. Almost always indicative of severe medical problems. The pressure itself can be responsible for further damage to the central nervous system by decreasing blood flow to the brain or by causing the brain to herniate (push through) the opening in the back of the skull where the spinal cord is attached.

**Intention to Treat:** A method of analysis for randomized trials in which all patients randomly assigned to one of the treatments are analyzed together, regardless of whether or not they completed or received that treatment.

**Masking:** An experimental method in which patients, caregivers and/or research staff do not know and cannot figure out which patients are receiving treatment and which the control (e.g. placebo). Also known as “blinding.”

**Monoplace chamber:** Type of HBOT chamber. Serves one patient at a time. Usually constructed of clear acrylic or metal (steel, aluminum) with acrylic viewports that allow for patient observation. Generally pressurized with 100 percent oxygen.

**Multiplace chamber:** Type of HBOT chamber. Serves more than one patient at a time. The entire chamber is pressurized with air, and each patient is given 100 percent oxygen through a facemask, tight-fitting hood, or endotracheal tube.

**Nonrandomized controlled trial:** Study design where treatments, interventions, or enrollment into different study groups are assigned by a process other than randomization. These groups are followed up for the variables/outcomes of interest.

**Observational study:** A study design in which the allocation or assignment of factors is not under the control of the investigator.

**Poor-quality study:** A study with the following characteristics: Groups assembled initially are not close to being comparable or maintained throughout the study; measurement instruments are unreliable or invalid or not applied at all equally among groups; outcome assessment is not masked; and key confounders are given little or no attention. For randomized controlled trials, no intention-to-treat analysis. See also good quality study, fair quality study.

**Qualitative research:** A kind of research that produces findings not arrived at by means of statistical procedures or other means of quantification. Generally examines people's words and actions in narrative or descriptive ways more closely representing the situation as experienced by the participants.

**Randomization:** Ideally, a process that ensures every member of a population has an equal chance to be included in the study's sample. Study patients are assigned to treatment or control groups without regard to any patient characteristics or study personnel desires or biases.

**Randomized controlled trial (RCT):** Study design where treatments, interventions, or enrollment into different study groups are assigned by random allocation rather than by conscious decisions of clinicians or patients. These groups are followed up for the variables / outcomes of interest.

**Retrospective comparison of cohorts:** A type of observational study. This study design begins with a group of individuals with a particular outcome and tests the hypothesis that some prior characteristic or exposure is more common in persons with the outcome than those without.

**Systematic review:** An organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific predefined criteria.

**Time-series:** An observational study in which an outcome is measured in the same group of patients at multiple points before, during, or after an intervention.

**Validity, external**: The extent to which the results of a trial provide a correct basis for generalizations to other circumstances. Also called "generalizability" or "applicability."

**Validity, internal:** The extent to which a study describes the "truth." A study conducted in a rigorous manner such that the observed differences between the experimental or observational groups and the outcomes under study may be attributed only to the hypothesized effect under investigation.

# Supplement. A Qualitative Assessment of Brain Injury, Cerebral Palsy and Stroke Patient, Caregiver and Clinician Values of Outcomes

## Introduction

In conjunction with the evidence report on hyperbaric oxygen therapy (HBOT), we conducted a qualitative research project involving focus groups to guide our evaluation of the outcomes assessed in the evidence. Qualitative research can be a valuable adjunct to evidence reports by broadening the scope of evidence-based medicine and "can help bridge the gap between scientific evidence and clinical practice."[1] Qualitative methods also offer "insight into the factors that shape lay and clinical behaviour."[2]

Our goal was to examine the relative importance of different outcomes to patients, caregivers, and clinicians, and how experience and attitudes influence the value they place on different outcomes. Specifically, we sought to answer the following questions:

1. What outcomes are most important to patients, caregivers, and clinicians?
2. Are there differences among groups of patients and caregivers and clinicians in the value placed on each outcome? If so, are these differences related to the degree and duration of improvement?
3. How much effort, discomfort, or risk would participants be willing to accept to achieve a short-term improvement?

## Methods

A Multiple Perspectives model, represented in the Figure, provided a framework for the collection and analysis of the data.[3, 4] In the figure, two overlapping ovals depict groups of people who hold different perspectives. The oval on the left represents "hyperbaric oxygen therapy experience," and the one on the right represents "brain injury, cerebral palsy, or stroke experience." The darkened area where the ovals overlap represents experience with HBOT and with brain injury, cerebral palsy, or stroke. The groups of people viewing their experiences and expressing their perceptions of them include six categories, labelled A through F. The rays pointing from each category to an oval or to the overlapping section of the circles indicate that these groups are viewing the objects within the ovals from their own perspectives. The individuals interviewed for our project were selected because they fit into one of these relevant groups. The results are descriptions of the views of each group about hyperbaric oxygen therapy; treatments for and recovery from brain injury, cerebral palsy, or stroke; or the intersection of the two.

Focus groups were the primary method for collecting data for this study.[5] Focus groups are group interviews where "several members of an aggregate are gathered together for a facilitated discussion about phenomena of import to them as a group."[6] Recognizing that there might be scheduling difficulties, because travel would be necessary for some interviewees, the researchers conducted individual interviews to augment the focus group data. These topical oral history

interviews, tape-recorded narrative accounts of past events experienced by those being interviewed,[7] provided in-depth descriptions of HBOT treatments over time. The data from the interviews therefore enriched the focus groups.

## Participant Selection

Focus group participants were selected based on either their experience with HBOT and/or their experience with one of the three disease states; brain injury, stroke or cerebral palsy. Participants who had experience with HBOT were divided into two categories: those with experience with *approved* uses of HBOT, such as clinicians working at hospitals that have hyperbaric chambers, and those who had experience with HBOT specifically for treatment of stroke, cerebral palsy, or brain injury. Participants who did not have experience with HBOT were chosen based on their experience with stroke, cerebral palsy, or brain injury. This group was divided into patients (or caregivers) and clinicians. The categories of participants and the number in each category are summarized in the Table. We recruited clinicians from a local freestanding chamber facility (Group B), nominations from technical experts (Group D), and Oregon Health & Science University (OHSU) faculty (Group F). We recruited patients and caregivers through OHSU clinics (Groups A, C) and from a local freestanding chamber facility (Group E).

**Table. Groups of patients or caregivers and clinicians.**

| | Patients or Caregivers | | Clinicians | |
|---|---|---|---|---|
| Medical condition | HBOT experience | No HBOT experience | HBOT experience | No HBOT experience |
| Brain injury, stroke, or cerebral palsy | N=7 (Group E) | N=4 (Group C) | N=3 (Group B) | N=2 (Group F) |
| Other conditions | N=1 (Group A) | | N=4 (Group D) | |

Participants were recruited and consent obtained following approved university human subjects protocols. Participants were paid honoraria and travel expenses, where applicable.

## Data Collection

We held five separate focus groups for participants in Groups B, C, D, E, and F. We also conducted six individual interviews:

- A patient in Group A.
- A stroke patient and her caregiver in Group E.
- A caregiver of a cerebral palsy patient in Group E.
- A caregiver of a brain injury patient in Group E.
- A clinician in Group B
- A clinician in Group D.

The research team developed the initial questions, which were designed to stimulate discussion about participants' experiences with brain injury and with HBOT treatment. We then developed interview guides so that appropriate questions would be asked, depending on whether

patients or clinicians were subjects. Questions were sometimes modified from one focus group to the next as experience was gained, which is typical of focus groups and the iterative nature of qualitative research.[8] As illustrations, the interview guides for three different focus groups and one of the individual interviews are shown in the Appendix E Attachment.

The focus groups were conducted as semi-structured interviews because, although the research questions needed to be addressed, we did not want discussion limited to those issues. Instead, we wanted individuals to raise issues of importance to them.

The six focus groups and six interviews were tape recorded and transcribed. Four of the focus groups were held on the Oregon Health & Science University campus in Portland, one was held at a local freestanding hyperbaric oxygen chamber facility, and one was held at a hospital with a chamber outside of Portland. The moderator for all sessions was a qualitative methods researcher with extensive interviewing experience. A second researcher took handwritten notes of both observations and discussion during each focus group. Each focus group session was two hours. The focus group moderator also conducted the interviews, four by telephone and two in person.

## Data Analysis

A grounded theory approach was used to analyze the content of the 12 transcripts. This means that the informants' own words were the starting point for the development of themes.[9, 10] The primary qualitative researcher read each line of each transcript, pulling out important words and phrases, which became codes that were written in the margins. As an example, one focus group generated 61 codes, such as "problems with insurance now," "functional measures are needed," and "have to balance risk and benefit." The total number of codes for all transcripts was approximately 500, and from these, the researcher developed lists of patterns and themes. Patterns are issues that occur frequently, and themes are groups of patterns that form a larger idea. For example, a pattern seen in transcripts of patient interviews was that mobility improvements are highly valued. This pattern, along with several other patterns such as vision and speech, ultimately became a theme, "physical improvements," in the Values of Patients section. The data (i.e., the codes) were entered into a spreadsheet so that the phrases could be easily grouped.

Several procedures served to assure that an accurate picture emerged from the data. A second qualitative methodologist who was not otherwise affiliated with the project reviewed all of the transcripts and did high-level coding and analysis paragraph by paragraph. During a series of meetings of the two qualitative researchers, final themes and sub-themes were developed. The other research team members, who often had been present during the interviews and focus groups, then reviewed these results. This review provided another means of ensuring that themes were accurately described. The expert panel also reviewed the results. Finally, the EPC Director, Dr. Helfand, reviewed the transcripts and the report. These various forms of critiques are all methods for assuring trustworthiness, the qualitative equivalent of validity.

# Limitations

Limitations of the study included difficulty in eliciting value judgments about HBOT from participants who had never experienced it. Scheduling focus groups for which participants needed to travel long distances was difficult but alleviated somewhat by the ability to do

interviews by phone. The nature of the interviews was different from the focus groups, in that synergy with others was not possible, but they had an advantage in that more detailed longitudinal information could be obtained. Another limitation was that participants familiar with HBOT who were nominated by HBOT clinicians tended to be strong supporters of the therapy. Finally, the individuals within each focus group were not homogenous. For example, interviewees in the focus groups of parents with children with cerebral palsy differed a great deal because their children's conditions varied so much.

# Results

## Values of Patients and Caregivers

### Benefits of HBOT

**Brain injury and Stroke**. In the brain injury and stroke focus groups, responses varied greatly, and patients mentioned a broad range of outcomes. Each of four participants identified a different problem as his or her major problem—pain, vision problems, seizures, and cognitive impairment. The outcomes valued by HBOT-treated and non-treated brain injury or stroke patients did not differ. Both groups valued frequently measured outcomes, such as cognitive improvements, speech, independence, physical improvements, less pain, short-term memory gains, ability to work, seizure reduction, smell and taste, dexterity, and psychological improvements. They also valued more subjective and less measurable attributes, such as feeling better, less pressure in the head, more positive attitude, easier to live with, decrease in drugs, more energy, greater awareness, and increased self-esteem.

**Cerebral palsy.** For cerebral palsy patients, the responses reflect that of parents and caregivers brain injury and stroke. The outcomes parents cited as most important were steps that indicated increased interaction with parents, such as saying "I love you" or smiling for the first time. Many commonly measured outcomes were also important to them, including cognitive abilities, vision, spasticity, eating, fewer medications, reduced seizures, speech, and walking. Less commonly measured outcomes were of similar importance: warmer hands and feet, smiling, improvements to the immune system, awareness, less autism, and bladder control. Parents said things such as "sucking from a straw was like a mountain," "putting more than two words together (in a sentence) was a big step," and she was "not as sick as she used to be," thanks to HBOT. Relaxing a hand and decreased drooling were also mentioned as meaningful improvements.

Parents of CP children treated with HBOT spontaneously raised the subject of single photon emission computed tomography (SPECT) scans in every interview or focus group, while parents of CP children not treated with HBOT did not mention it, and when asked, had not heard of SPECT scans. The CP parents with HBOT experience believed the technique provides real evidence of improvement. One stated, "you can see that area of the brain working" [on a SPECT scan]. Another said, "That's why the SPECT scan is so critical. The SPECT scan can document something that makes it undeniable. This is the before. This is the after." This person went on to say that SPECT scans provide the evidence needed to show that HBOT is a "treatment necessary to correct (a physiologic deficit)," and that insurance should therefore cover payment.

There were other differences between parents whose children had and had not experienced HBOT. When asked about temporary regression of symptoms after any therapy, the CP parents without HBOT experience said that improvement for a week may not be worth the effort of seeking treatments, but improvement for 6 months would make it worthwhile. The parents of CP children with HBOT experience would definitely seek more HBOT treatments for either short- or long-term gain or for any degree of improvement as long as they felt the treatments were at a safe pressure level.

### Harms and Risks of HBOT

For parents who did not use HBOT, the possibility that their children might undergo risk without benefit was of the highest importance. This attitude seemed to be related to their previous experience with conventional and unconventional therapies.

When asked about the downside of HBOT, patients and caregivers who had HBOT experience did not speak of risks. They tended to talk about the time driving for therapy and other ancillary negatives. One parent had broken an eardrum during HBOT treatments for his son when he entered the chamber, but he did not mention this in the context of risk.

Patients and caregivers (as well as clinicians) feared that the sale of chambers to individuals, often over the Web, is dangerous. Parents described other parents with "chambers in their basements and they have no clue what to do with them." They said of one parent, "People drive to dive in her garage." The parent movement, they said, "has taken on a life of its own…we've got to make it affordable. We have to make it safe."

## Values of Clinicians

### Benefits of HBOT

Clinicians valued many of the same outcome cited by patients and caregivers, for example, quality of life, cognitive abilities, speech, and motor function. Clinicians pointed out that interactions and independence are highly valued. Clinicians emphasized measurable improvements and objective measures more than did patients or caregivers. They consistently pointed out the variation in the severity of illness among patients, ranging from those who need constant total care to those who are relatively independent.

Unlike some parents, who expressed a strong belief that SPECT scans are valuable indicators of improvements in their children's conditions, clinicians were not so sure. We were told that SPECT scans might not measure outcomes "relevant to function" or measure "a clinical correlate." One clinician who used HBOT said that he has seen "success that is observable, objective, measurable, you know, by a variety of different physical therapy test methods," and he did not use SPECT scans because "I'm not running a big research facility here and there's very little money for it."

Clinicians were able to accurately identify the values parents and patients would have, e.g., they understood how important a child's ability to walk with flat feet for the first time might be to the parent of a CP child. Even when clinicians cited measurable outcomes as being important, they always added that less measurable outcomes, such as the patient interacting more with caregivers, were also extremely important.

### Harms and Risks of HBOT

Clinicians who used HBOT for brain injury, stroke, or cerebral palsy and those who did not viewed the harms and risks of HBOT differently. Clinicians who did not use HBOT for brain injury described numerous risks, including financial risks for patients and families. They warned against "people wishing to prey upon families and patients" and disliked the idea of "people taking advantage of patients." The physical risks they mentioned included problems with ears and sinuses, claustrophobia, oxygen toxicity, seizures, blood sugar, vision, and fire. They gave detailed descriptions of the risks along with probabilities of adverse events. Those who used HBOT for conventional indications did not allow family members into the chambers at all because of risks. These clinicians believed that "basement/garage chambers are a disaster waiting to happen.

The HBOT clinicians who treat brain injury, cerebral palsy, or stroke considered the risks to be minimal or did not mention them at all.

## Patterns and Themes

There were four overarching themes that emerged from the data: 1) View of Medicine, 2) Attitudes toward Risk, 3) Hope, and 4) Politics.

### Views of Conventional Medicine

Patients and caregivers were frustrated with conventional medicine, but they varied in the degree of frustration. Those who had not experienced HBOT had dedicated themselves to various types of therapies, such as physical, speech, and occupational therapies and often believed that "the outcomes are so miniscule." For the particular conditions at issue here, the trial and error approach seemed like a difficult and never-ending journey. The difficult part of the journey, we were told, is seeing your child working so hard and in pain. Botox treatments for the CP patients were cited as one of the worst aspects of their experience, with surgery a close second because it "is a life-consumptive event," engulfing the entire family. When asked about the value of a therapy such as HBOT to help their children, these parents replied that they would want to see real evidence for its value before they would submit their children to one more kind of therapy. One mother stated that the family had been through so much with different therapies that "now I would thoroughly check it out and if I knew it would help, I would dedicate any amount of time to it." One parent said that doctors "are from a different world," and only a parent of a similar child would truly understand what her life is like.

Patients who had sought out HBOT had much stronger feelings about conventional medicine than those who had not used HBOT. They believed they had exhausted the limits of conventional medicine and moved on to alternative therapies. Most patients were using several complementary and alternative medicine therapies at once, which made it difficult to judge whether HBOT or something else was making a difference. Some caregivers believed that conventional medicine is sabotaging HBOT, undermining efforts to prove its efficacy. These patients and caregivers were more willing to trust strongly worded testimonials and case studies than scientific evidence, partly because of a lack of trust in the medical establishment.

The names of a few physicians were consistently invoked as having gained the trust of these patients and caregivers. Parents of children who had been treated with HBOT believed that

SPECT scans provide evidence of improvement, even if that improvement is not correlated with a clinical improvement.

Patients who had sought HBOT tended to have a large medical vocabulary of terms relating to the relevant condition. The terminology was retained from information they gathered, but the meaning was sometimes lost. Often, the terms were used in new ways that seem to fit the belief systems of the caregiver. For example, one parent equated her CP child's brain to a Pepsi: "you put a body inside a hyperbaric chamber and submerge it in a hundred percent oxygen with that pressure, every cell in that body is saturated with that oxygen. Most importantly the spinal fluid that goes up the back around the brain and it bathes the brain. It immediately starts breaking that calcification down."

Clinicians differed in their view of conventional medicine as well. The clinicians who did not use HBOT for brain injury, stroke, or CP wanted to see clear evidence that it works and does no harm: they would carefully weigh the risks and benefits. They "love to see people get better but need real evidence." These clinicians pointed out that many therapies in general use have not been proven completely useful and are sometimes prescribed so that "parents feel more engaged." They stated that they would like to see good studies on HBOT and were aware of and valued the 2001 Canadian study on cerebral palsy and HBOT.[11]

The clinicians who used HBOT for brain injury, cerebral palsy, or stroke considered their own experience to be clear evidence, and they could tell stories of their own patients as testimony. Two focus groups produced 15 stories of dramatic improvements after HBOT treatments. These clinicians stated that they would like to see good studies done, but they did not talk about evidence as often as the other clinicians. They spoke about other alternative therapies more often than clinicians who did not use HBOT and consistently emphasized the value of combining HBOT with nutrition and other wellness approaches. They also held strong beliefs in the benefits of diet, vitamins, stress reduction, and other therapies, with HBOT just one of many modalities in a holistic approach to treatment.

### Health Information Seeking

This theme encompasses a wide range of activities, from phoning a society to requesting a book about cerebral palsy, which becomes "my first lifeline" after a parent learned her child had CP, to participating in online communities of patients, caregivers and supporters of HBOT.

Patients and caregivers unanimously said that they had done their own research about their conditions. All but one was active in networking online. The parent who said that doctors are from another world also said she actively asked other parents of children like hers for their advice. The CP parents said that parental decision-making is "like playing God," and that any help they could get was wonderful. The HBOT-supporter parents had active online communities with a listserv, large organizations of parents, and newsletters.

Clinicians used online resources as well. The clinicians who used HBOT for brain injury and stroke had a clear presence on the Web, and they have used the media, including television, to disseminate information about HBOT.

### Hope

Faith and prayer were mentioned by both clinicians and patients and caregivers as therapies in their own right for those with brain injury, stroke, or cerebral palsy. However, the HBOT

caregivers volunteered many stories about miracles. HBOT was referred to as "God's medicine," and one parent said, "God's put the chamber here for the kids to be helped." Miracle stories from both parents and clinicians were many. One example was about an aphasia patient who "started spontaneously talking again" after 20 HBOT treatments, and another was a story about a stroke survivor who "lost the cane 3 days after starting the treatments." The caregivers who had not experienced HBOT spoke about little steps, about the small bits of progress they hoped their children would see. For that hope, they lived family lifestyles full of activity involving one therapy after another.

### Politics

This term is being used broadly to signify politics at the national level and its relation to HBOT, politics among and within societies related to HBOT, and the politics of insurance and getting treatment paid for. The clinicians and patients and caregivers who had no experience with HBOT were unaware of such politics. However, clinicians and patients and caregivers with HBOT experience were extremely vocal about it. Those with HBOT experience for approved conditions knew about efforts at the national level to gain funding for clinical trials for HBOT for brain injury, cerebral palsy, or stroke, about the efforts to have insurance pay for HBOT treatments, and about the online communities of HBOT supporters.

Patients and caregivers with HBOT experience for brain injury, stroke, or cerebral palsy were pleased that the present systematic review was being done, and they were constantly aware that what they said might influence funding. Many were involved in advocacy for funding for HBOT therapy for brain injury, cerebral palsy, or stroke, clinical trials, and attention to the safety of chambers. This group distrusted the medical establishment, however, and did not believe that unbiased clinical trials could be conducted. One parent said it "is sad that our country would deprive us of something and we would have to go to those extremes" [such as going to another country] to get HBOT therapy.

## Conclusions

We undertook this study to ensure that our systematic review sought evidence about outcomes that patients and caregivers care about. We also wanted to test the hypothesis that differences in attitudes about short-lived or small responses to therapy might explain differences in views about the effectiveness of HBOT.

We found that commonly studied outcomes, such as motor and speech function, are important to patients and caregivers. However, we also found that many outcomes that are not routinely measured in studies are of equal, if not greater, importance to patients and caregivers.

Our results did not reveal any consistent differences among the groups of patients or clinicians in how they valued small or temporary improvements. Rather, the results suggest that what we might consider to be a small or temporary improvement in function can have a large impact on caregiver burden. Discussions with caregivers revealed the most dramatic differences between what studies measure and what participants valued. Functional differences that might seem small or insignificant on standardized functional scales have a large impact on caregivers. Put differently, even if the standard measurement instruments are sensitive to small changes in

function, they may be insensitive to the impact of these changes on caregivers and on the family as a whole.

All focus groups (clinicians and patients and caregivers with and without HBOT experience) agreed on the need for more evidence about the efficacy and safety of HBOT for brain injury, stroke, and cerebral palsy. For patients and caregivers with HBOT experience, however, this need is tempered by distrust of the medical establishment. Without trust, it is questionable whether or not they will believe that the research was conducted in good faith.

Patients and caregivers who had not used HBOT are skeptical of the benefits and concerned about the potential adverse effects. This skepticism arises from their experience with other treatments for which the expected benefits never materialized or were not worth the harms, inconvenience, cost or risk. They will continue to be skeptical unless better-quality studies are done.

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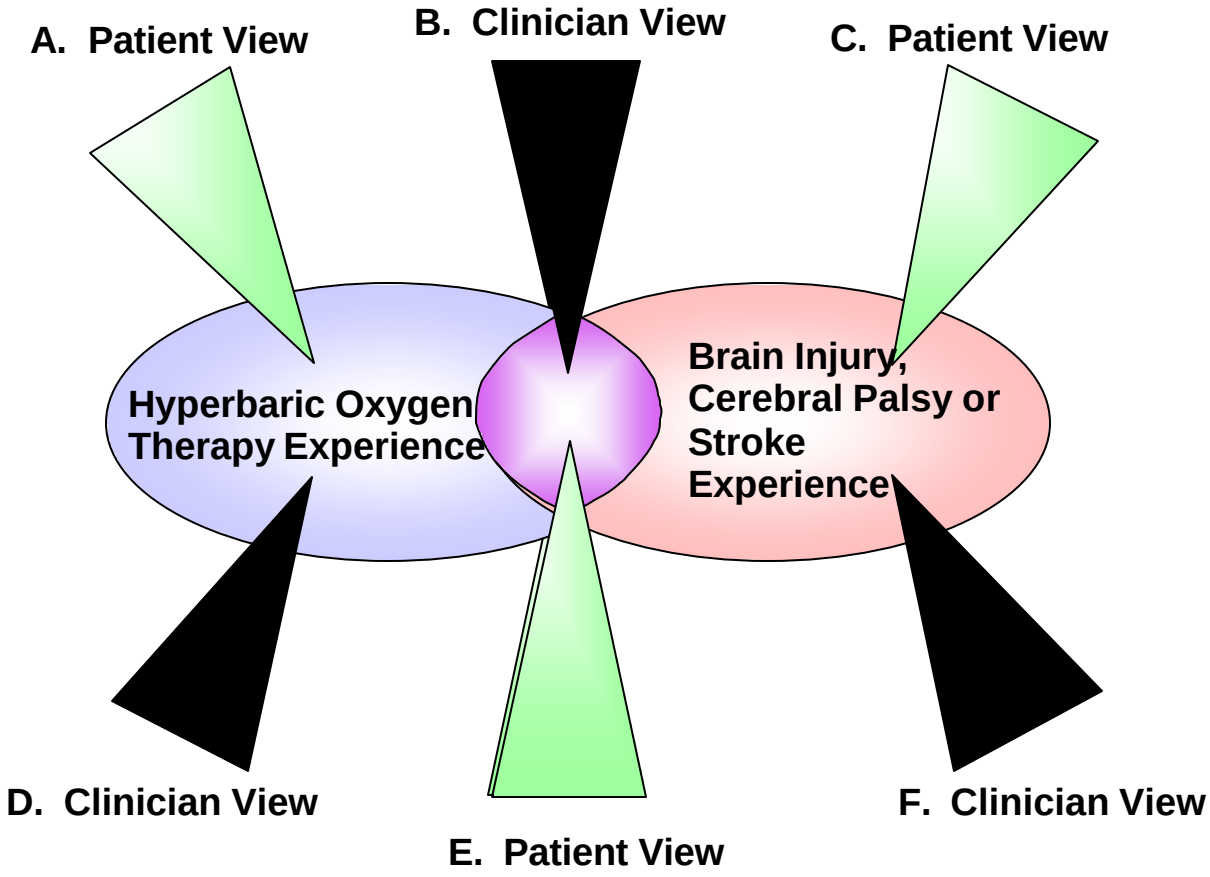
**Supplement Figure**



# Supplement Appendix. Interview Guides

## Guides for Focus Groups

Brain injury or stroke patients with no HBOT experience (February 23, 2002)

Introduction of study personnel
Purpose of focus group and importance of their roles
Signing the consent forms
Introductions: name, their injury (what it was, date, outcome)
Ground rules: all discussion voluntary, no criticism, confidentiality assured, try to represent peers

Exercise: write down the five worst things about their episode's aftermath; five positive things? Go around and list them

List? What outcomes do they desire? Describe a really good outcome

Which are most important? Make up a scale and rate them (really important, moderately or less)

How important is duration of each outcome? For what outcomes would you be willing to accept only short-term outcomes?

What might your caregiver say?
Inconveniences and discomforts

Imagine that there is a therapy that can be delivered in a submarine that is perfectly safe. How would you feel about entering the submarine? On a daily or weeky basis?

Let me summarize what we've learned today: Have we missed anything?

Brain injury or stroke patients/caregivers with HBOT experience (March 11, 2002)

Signing the consent forms
Introduction of study personnel
Purpose of focus group and importance of their roles
Ground rules: all discussion voluntary, no criticism, confidentiality assured, try to represent peers

Introductions: name, their injury (what it was, date, outcome), therapies besides HBOT they've tried

Exercise: write down the five worst things about their situation; five positive things?
Go around and list them
List? What outcomes do they desire? Describe a really good outcome

What outcomes did HBOT produce?
Which are most important? Make up a scale and rate them (really important, moderately or less)

Outcome if short term Importance 1 to 3
Outcome if long term Importance 1 to 3

How important is duration of each outcome? For what outcomes would you be willing to accept only short-term outcomes?

What might your child say?
Inconveniences and discomforts

Let me summarize what we've learned today: Have we missed anything?

Clinicians with HBOT experience (March 15, 2002)
Signing the consent forms
Introduction of study personnel
Purpose of focus group and importance of their roles
Ground rules: all discussion voluntary, no criticism, confidentiality assured, try to represent peers
Introductions: name, their background that led to interest in HBOT
How did interest develop?

Upsides and downsides
The good and bad for each condition
Inconveniences and discomforts

What outcomes do they desire? Describe a really good outcome
What outcomes did HBOT produce? Listen for coordination, weakness, walking, cognition

Which are most important? Make up a scale and rate them (really important, moderately or less)
Outcome if short term Importance 1 to 3
Outcome if long term Importance 1 to 3

How important is duration of each outcome? For what outcomes would you or patients or caregivers be willing to accept only short term outcomes?

The SPECT scan issue

Focus on CP and stroke issues

Future research suggestions

Let me summarize what we've learned today: Have we missed anything?

## Guide for Individual Interviews

(Note: This is a generic guide; these questions were always covered, but more specific questions and probing questions were also asked in addition to these.)

Introductions

Discuss the consent form

Purpose of project and interview

Can you start out by telling me what led up to your/his/her first HBO treatment?

Had you heard about HBO before? How did you hear about it?

What was the course of treatment like? How many? Kind of chamber? Did caregiver accompany? Feelings about it?

What difference did you notice and at what point in treatment? What was the most exciting breakthrough, if any?

Were there any discomforts or inconveniences?

What other therapies were you undergoing at the same time? Prior to HBO?

One of the things we're trying to find out is how people value the outcomes of HBO. What good does it do and what is it worth to you? To your caregiver or child?

Let me summarize what we've learned today: have we missed anything?