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.