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My wife Carolyn and our three children, Connor, Riley, and Ellen love the outdoors. Sailing, kiting, windsurfing, snowboarding, and golf are favorite activities.

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Editorial

Hyperbaric oxygen: A potential new therapy for leukemia?

Keywords: Hyperbaric oxygenation; Leukemia; Apoptosis; Cell; Proliferation; Neoplasms

Hyperbaric oxygen (HBO_2) therapy is the administration of 100%-inhaled oxygen to patients at increased atmospheric pressure. The amount of oxygen bound to circulating hemoglobin is very similar whether a patient breathes air at sea level or breathes 100% oxygen at increased pressure. In contrast, while the partial pressure of oxygen dissolved in plasma is usually 100 mm Hg in a person breathing air at sea level, it can exceed 1000 mm Hg in a person during an HBO_2 treatment. Consequently, HBO_2 enhances oxygen delivery to cells throughout the body. HBO_2 is a proven, effective treatment for patients with carbon monoxide poisoning, decompression sickness, and arterial air embolism. There is also evidence supporting the use of HBO_2 to treat gas gangrene, osteomyelitis, radiation tissue damage, and compromised skin grafts as well as to enhance the healing of selected problem wounds [1].

Oxygen is a potential anticancer therapeutic. Mammalian cells require oxygen to proliferate and, under certain conditions, cells also need oxygen to undergo apoptosis. In cancer, the balance between cell proliferation and apoptosis is not in equilibrium. Due to their rapid growth and limited angiogenesis, solid tumors have areas where oxygen concentrations are very low. While hypoxia probably slows tumor growth, it also causes these tumors to be resistant to the tumoricidal effects of radiation. Based upon these observations, HBO_2 was used successfully over 30 years ago as a radiosensitizer in clinical trials of head and neck cancer [2] and cervical cancer [3] performed by the British Medical Research Council. In vitro studies have demonstrated that HBO_2 can also increase the tumoricidal effects of chemotherapeutic agents [4]. Due to the cumbersome nature of administering chemotherapy and especially radiation to patients in hyperbaric chambers, HBO_2 therapy for cancer may have been prematurely abandoned.

Cells use oxygen as a terminal electron acceptor in the process of generating ATP in their mitochondria. Reactive oxygen species (ROS) are promiscuous byproducts of this reaction. When ROS react with macromolecules (such as proteins, lipids, and DNA), the initial reaction generates a second radical, which then reacts with another macromolecule, creating a radical-forming cascade. The overall balance between intracellular ROS production and antioxidant defense mechanisms determines the redox status of a cell. By increasing the amount of oxygen dissolved in the extracellular space both in vitro and in vivo, hyperoxia at ambient pressure and HBO_2 enhances intracellular oxygen levels and ROS [5]. The resulting milieu can cause the intracellular oxidative activities to overwhelm the reducing equivalents, thereby placing cells in a state of oxidative stress and activating stress signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway [6]. Although the molecular mechanisms whereby ROS induce these pathways are still uncertain, activating these pathways results in apoptosis. While hyperoxia and HBO_2 usually exert similar effects, in some models their effects differ, suggesting that increasing atmospheric pressure does more than simply further enhancing hyperoxia.

In this issue of Leukemia Research, Chen et al. report that HBO_2 induces apoptosis in the Jurkat T-cell leukemia and the NCI-H929 myeloma cell lines [7]. These findings confirm our earlier report demonstrating that HBO_2 induces spontaneous, radiation-induced, and chemotherapy-induced apoptosis in Jurkat and HL-60 promyelocytic leukemia cells [8]. These experiments demonstrate that HBO_2 is pro-apoptotic in hematopoietic cells, a phenomenon that merits confirmation in other leukemia cell lines. In contrast to the hematopoietic cell lines, neither Chen et al. nor our group were able to show that HBO_2 affects apoptosis in the non-hematopoietic A549 lung carcinoma and MCF-7 breast adenocarcinoma cell lines and in patient-derived benign and malignant mammary epithelial cells immortalized by transfection with the human papilloma virus E6 oncogene [9]. The molecular correlate of these cellular phenomena is Chen's intriguing observation that HBO_2 activates the pro-apoptotic MAPK pathway in hematopoietic cells, but not in non-hematopoietic cells.

In addition to stimulating apoptosis, oxidative stress can also trigger anti-apoptotic pathways. Not unexpectedly, Chen et al. observed that the anti-apoptotic ERK pathway is

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down-regulated or unaffected in HBO_2-exposed hematopoietic cells. While this group did not explore the status of ERK in HBO_2-exposed non-hematopoietic cells, Lee et al. have reported that HBO_2 activates ERK in human umbilical vein endothelial cells [10]. In addition, it is notable that oxidative stress turns on calcium/calmodulin-dependent kinases (and thereby ERK) [11] and that H_2O_2 induces MCF-7 cell apoptosis only if the cells are incubated in the presence of a calcium/calmodulin-dependent kinase inhibitor [12].

In addition to influencing apoptosis, HBO_2 can also affect cell proliferation. HBO_2 inhibits proliferation in some models and stimulates it in others. Studies showing HBO_2's antiproliferative effects led to the aforementioned 1970s clinical studies showing that HBO_2 slowed tumor progression. However, because HBO_2 enhances proliferation in some in vitro models, there are also concerns that HBO_2 could promote cancer progression in vivo [13]. To address this possibility, Feldmeier et al. reviewed human and animal studies examining the effect of HBO_2 on tumor progression [14]. These authors concluded that HBO_2 treatment has a neutral effect on solid tumor growth. There were an insufficient number of studies available for them to reach any conclusions regarding the in vivo effects of HBO_2 on hematopoietic cancers.

The effects of HBO_2 on cellular function are also influenced by the extracellular environment. Because HBO_2 produces much higher oxygen tensions in cell culture media than in vivo, it is possible that HBO_2's effects on apoptosis and proliferation are in vitro phenomena. For this reason, human primary leukemia cells should be transplanted into immunodeficient mice, the mice exposed to HBO_2, and apoptosis measured. If HBO_2 causes leukemia cell apoptosis in these animal models, primary human leukemia cells could then be exposed to HBO_2 ex vivo, and the cell death pathways further studied to provide more insight into how HBO_2 might be used against leukemias.

In summary, the finding that HBO_2 promotes leukemia cell apoptosis prompts us to reconsider using HBO_2 to treat cancer. Because it suppresses proliferation, HBO_2 has been used to treat solid tumors. Because it promotes apoptosis, HBO_2 merits further study as a novel treatment for leukemias, either alone or as an adjuvant to chemotherapy.

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Delayed hyperbaric oxygenation is more effective than early prolonged normobaric hyperoxia in experimental focal cerebral ischemia

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Abstract

Hyperbaric (HBO) and normobaric (NBO) oxygen therapy have been shown to be neuroprotective in focal cerebral ischemia. In previous comparative studies, NBO appeared to be less effective than HBO. However, the experimental protocols did not account for important advantages of NBO in the clinical setting such as earlier initiation and prolonged administration. Therefore, we compared the effects of early prolonged NBO to delayed HBO on infarct size and functional outcome. We also examined whether combining NBO and HBO is of additional benefit. Wistar rats underwent filament-induced middle cerebral artery occlusion (MCAO) for 150 min. Animals breathed either air, 100% O_2 at ambient pressure (NBO; initiated 30 min after MCAO) 100% O_2 at 3 atm absolute (HBO; initiated 90 min after MCAO), or a sequence of NBO and HBO. Infarct volumes and neurological outcome (Garcia score) were examined 7 d after MCAO. HBO ($174 \pm 65\,mm^3$) significantly reduced mean infarct volume by 31% compared to air ($251 \pm 59\,mm^3$) and by 23% compared to NBO treated animals ($225 \pm 63\,mm^3$). In contrast, NBO failed to decrease infarct volume significantly. Treatment with NBO + HBO ($185 \pm 101\,mm^3$) added no additional benefit to HBO alone. Neurological deficit was significantly smaller in HBO treated animals (Garcia score: 13.3 ± 1.2) than in animals treated with air (12.1 ± 1.4), but did not differ significantly from NBO (12.4 ± 0.9) and NBO + HBO (12.8 ± 1.1). In conclusion, HBO is a more effective therapy than NBO in transient experimental ischemia even when accounting for delayed treatment-onset of HBO. The combination of NBO and HBO results in no additional benefit.

Keywords: Hypoxia; Neuroprotection; Stroke; Experimental ischemia

Improving tissue oxygenation in ischemic stroke has been considered a promising therapeutic strategy for many years. The majority of experimental studies have been performed with hyperbaric oxygen treatment (HBO). Despite positive results in experimental focal cerebral ischemia [14,24–28,30], the effectiveness of HBO in the treatment of acute ischemic stroke in patients remains controversial [4,16]. Disappointing results of clinical pilot studies [1,17,19], potential side effects of HBO [3,5,16], and limited availability of HBO chambers are major limitations. Recent experimental studies suggest that normobaric hyperoxia (NBO) has substantial neuroprotective effects in focal cerebral ischemia [6,11,12,21–23]. NBO has several advantages compared to HBO [21]. Importantly, NBO therapy could be initiated earlier after stroke-onset by emergency medical personnel with only minimal risk.

The efficacy of NBO and HBO has been compared directly only in a limited number of studies in focal cerebral ischemia. In most experiments, HBO showed a significantly stronger neuroprotective effect than NBO. The interval between onset of ischemia and initiation of oxygen therapy is an important factor determining its effectiveness [14,30]. In the previous studies, however, NBO was administered for the same duration and initiated after the same interval after ischemia-onset as HBO [25–28], although this experimental design does not reflect the time-advantage that can be expected for initiation of NBO in the clinical setting. Another interesting approach may be to com-

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bine the effects of both oxygen modalities sequentially, but this aspect has received only little attention so far [27]. The main purpose of the present study was to compare the effects of early initiated NBO to delayed HBO treatment on infarct size and neurological outcome in rats after transient focal cerebral ischemia. We hypothesized that initiating NBO earlier than HBO could compensate for inferiority of NBO in direct comparison of both therapies. We also addressed the question whether the combination of both therapies is superior to administration of NBO or HBO alone.

All experiments were performed on male Wistar rats ($n = 72$) weighing 300–350 g (Charles River, Germany) and approved by the local and regional governmental animal care authorities. Using a face mask, anaesthesia was induced with 4% halothane in O_2 and continued with 0.8–1.2 % halothane in a 70/30 mixture of nitrous oxide/oxygen under spontaneous respiration. During surgery, temperature was continuously monitored with a rectal probe and maintained at 37 °C with a thermostatically controlled heating pad. The femoral artery and vein were cannulated with PE-50 polyethylene tubing for continuous monitoring of arterial blood pressure and heart rate, to provide samples for blood gas measurements and to inject the MR–contrast agent. Focal cerebral ischemia was induced using the reversible filament occlusion model as introduced by Longa et al. [13] with some modifications as previously described [26]. After placement of the silicone coated filament and closure of the neck, rats were placed into a MRI scanner (Bruker Biospec, 2.35 T). Perfusion-weighted imaging (PWI) was performed to ensure hypoperfusion in the territory of the occluded MCA in all animals (see below). After PWI, rats were allowed to wake up. All animals were subjected to ischemia of 150 min duration. Treatment was performed according to one of four treatment protocols to which animals were randomly assigned (Fig. 1). Animals breathed either air, 100% O_2 at ambient pressure (NBO), 100% O_2 at 3 atm absolute (ata; HBO), or a sequence of NBO and HBO (NBO + HBO group). In the NBO group, NBO was initiated 30 min after MCAO and was continued for 120 min during ischemia plus 180 min during reperfusion. In the HBO group, HBO was begun 90 min after ischemia-onset and performed for 60 min. After reperfusion, these animals received no further therapy and breathed room air. In the NBO + HBO combination group, rats received NBO 30 min after onset of ischemia for a period of 60 min followed by HBO for 60 min plus 180 min of NBO during reperfusion. In all groups, a PWI MRI was performed just after removal of the filament to verify successful reperfusion in all animals. Animals were examined in a 2.35 T MRI scanner (Biospec 24/40, BRUKER Medizintechnik Ettlingen, Germany) with a previously described configuration and protocol [10]. For perfusion-weighted imaging (PWI), we used a gradient-echo echo-planar imaging (GE-EPI) sequence (repetition time = 1 s, echo-time = 15 ms, 20 repetitions with a time resolution of 1 s/image data set) for monitoring the bolus passage of 1 mmol/kg of a paramagnetic contrast agent (Omniscan, Nycomed Amersham, Oslo, Norway). For analysis of PWI during ischemia and after reperfusion, the relative cerebral blood volume (rCBV) and the relative mean transit time were calculated in two predefined regions of interest in the parietal cortex and the striatum in both hemispheres from the signal-time-curve determined from the PWI data set as previously described [9].

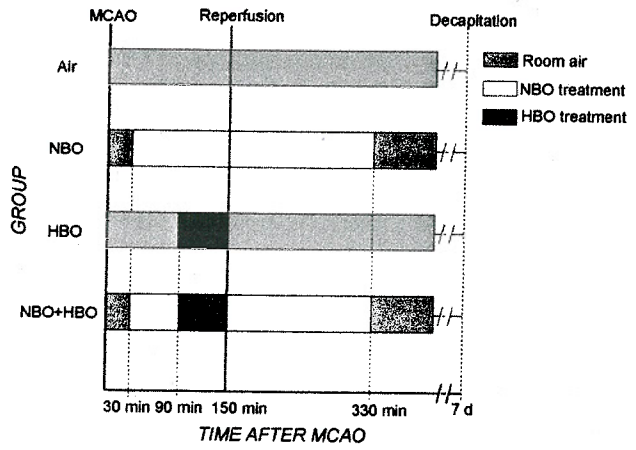

Fig. 1. Schematic overview of the experimental protocols.

Seven days after ischemia, rats were deeply anesthetized and transcardially perfused with 100 mL of heparinized saline. Brains were rapidly removed, frozen in isopentane and stored at −80 °C. For determination of infarct size, 20 μm coronal sections were cut at 400 μm intervals and stained with the high-contrast silver infarct method as previously described [29]. The public domain Scion image program was used for analysis of infarct size. No correction for focal edema was necessary at 7 d after ischemia.

Neurological deficit was graded 7 d after ischemia using a scale ranging from 3 to 18 introduced by Garcia et al. [7] for filament-induced MCAO in rats. On this scale, lower scores represent greater deficits. Scores were assessed by an observer blinded to experimental groups.

All values are expressed as mean ± standard deviation (S.D.). For comparison of physiological values, infarct volumes and MRI data, ANOVA was used followed by post hoc Fisher's protected least significant difference test. Between-group differences of behavioral scores were analysed with the Mann–Whitney U-test. All analyses were performed using SPSS analysis software. A p-value < 0.05 was considered statistically significant.

Physiological parameters before MCAO and 5 min after treatment were not significantly different between the air group and the different oxygen treatment groups except for arterial pO_2 (Table 1). Arterial pO_2 could not be measured during HBO treatment in the chamber. Perfusion deficit on MRI after MCAO in cortex and striatum did not differ among groups. Cortical rCBV (ischemic/nonischemic) was 0.57 ± 0.13 in the air, 0.54 ± 0.14 in the NBO, 0.60 ± 0.17 in the HBO group, and 0.62 ± 0.21 in the NBO + HBO combination group. Thus, all groups underwent ischemia of the same severity. Similarly, reperfusion after filament removal did not differ significantly among groups (data not shown).

Mortality did not differ significantly among the experimental groups during the 7 d observation period. In each of the air, NBO, and NBO + HBO combination treated groups three rats died, whereas only two rats died in the HBO group. Postmortem

Table 1
Physiological Parameters

	Air	NBO	HBO	NBO + HBO
Baseline				
pO_2 (mmHg)	136 ± 13.2	131.9 ± 13.5	136.9 ± 11.7	134.7 ± 8.9
pCO_2 (mmHg)	41.9 ± 4.6	41.8 ± 3.6	41.4 ± 3.4	43.4 ± 4.7
pH	7.45 ± 0.04	7.44 ± 0.03	7.45 ± 0.03	7.43 ± 0.04
Temperature (°C)	37.4 ± 0.3	37.2 ± 0.2	37.3 ± 0.2	37.3 ± 0.3
MAP (mmHg)	87.6 ± 7.9	88.7 ± 6.5	89.3 ± 9.4	86.4 ± 8.2
HF (bpm)	435 ± 46	433 ± 35	442 ± 49	429 ± 41
Reperfusion				
pO_2 (mmHg)	121.2 ± 19.8	385 ± 25.7*	570.3 ± 36.6*'**	546 ± 49.3*'**
pCO_2 (mmHg)	43.2 ± 4.2	44.7 ± 5.2	40.5 ± 5.8	41.6 ± 5.1
pH	7.39 ± 0.03	7.41 ± 0.03	7.42 ± 0.04	7.40 ± 0.03
Temperature (°C)	37.7 ± 0.3	37.6 ± 0.3	37.6 ± 0.4	37.5 ± 0.4

Except for arterial pO_2 after reperfusion, there were no significant differences in physiological parameters between groups (*$p < 0.05$ compared to air; **$p < 0.05$ compared to NBO; ANOVA and post hoc Fisher's protected least significant difference test).

examination of the animals which all died within the first 48 h after ischemia revealed massive brain edema with signs of uncal herniation as the most likely cause of death. These animals were not included in further data analysis.

Mean total infarct volumes were significantly smaller in HBO treated animals ($174 \pm 65\,mm^3$) than in animals treated with air ($251 \pm 59\,mm^3$) or NBO ($225 \pm 63\,mm^3$). Thus, HBO induced a 31% reduction of mean infarct volume compared to air despite a delay of treatment initiation (Fig. 2). In contrast, mean total infarct volume of NBO treated animals was not significantly smaller than of animals treated with room air. Treatment with NBO + HBO ($185 \pm 101\,mm^3$) resulted in a 26% reduction of mean infarct volume compared to air. Comparison of infarcted cortical and subcortical regions showed a significant reduction of mean cortical infarct volume in the HBO group compared to air ($79 \pm 49\,mm^3$ versus $132 \pm 37\,mm^3$) and to NBO ($117 \pm 54\,mm^3$). Mean cortical infarct volume of HBO + NBO treated animals ($83 \pm 58\,mm^3$) was significantly lower than of animals treated with air. There were no significant differences observed between mean subcortical infarct volumes among the groups, although a trend towards reduction was noticed between mean subcortical infarct volumes of HBO and air ($94 \pm 33\,mm^3$ versus $119 \pm 41\,mm^3$; $p = 0.08$). Mean subcortical infarct volumes were $108 \pm 34\,mm^3$ for NBO and $101 \pm 52\,mm^3$ for NBO + HBO.

Behavioral deficits evaluated 7 d after MCAO appeared to depend on the treatment strategy, being most severe in the air group (12.1 ± 1.4), followed by the NBO (12.4 ± 0.9), the NBO + HBO (12.8 ± 1.1), and finally the HBO group (13.3 ± 1.2) (Fig. 3). At a statistical significance level, though, only the HBO group showed a better outcome compared to air treatment. Absolute mean scores were rather high because the deficits measured by the Garcia scale had already improved 7 d after MCAO.

The findings in the present study may be of relevance for the translation of oxygen therapy from the experimental into the clinical setting. Consistent with previous studies from our and other groups [14,24–26,28], intraischemic HBO reduced histological infarct size and improved neurological outcome in rats subjected to transient focal cerebral ischemia. In contrast

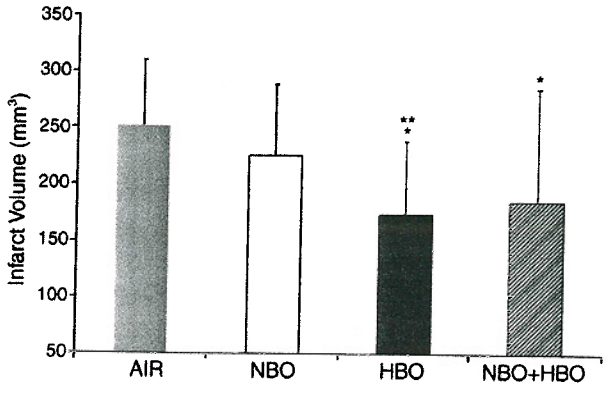

Fig. 2. Infarct volumes on silver stained sections 7 d after MCAO. HBO decreases infarct volume compared to air and NBO. Combination of HBO and NBO decreases infarct volume significantly compared to air, but difference was not significant compared to NBO treated animals (*$p < 0.05$ compared to air; **$p < 0.05$ compared to NBO; ANOVA and post hoc Fisher's protected least significant difference test).

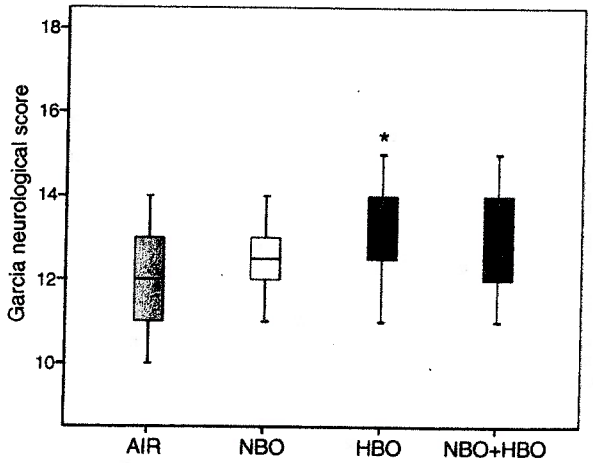

Fig. 3. Neurological deficit graded on the Garcia scale. HBO decreases neurological deficit compared to air and NBO (*$p < 0.05$ compared to air; Mann–Whitney U-test). NBO and combination of NBO and HBO (NBO + HBO) do not improve neurological outcome compared to air ($p > 0.05$; Mann–Whitney U-test).

to most previous studies, the delay until initiation of HBO was sufficiently long in the present study to be of significance for a substantial subgroup of acute stroke patients. Other authors have reported protective effects of HBO in rodent transient ischemia when treatment was started up to 6 h after ischemia-onset [2,14], but in these studies HBO was performed during the reperfusion period after early recanalization. When we examined longer time windows necessitating an MCA occlusion time of 4 or even 5 h, mortality became excessively high in all groups indicating a ceiling effect in the filament model which produces large hemispheric infarcts.

Although there is also accumulating evidence for a protective effect of NBO in cerebral ischemia [6,11,12,21–23], the available data suggest that its time window is short [22], that its effectiveness is inferior to HBO in transient [25,26,28] and limited in permanent focal ischemia [27]. Relative ineffectiveness of NBO compared to HBO in previous experimental studies may have been caused by starting both treatments after an identical interval although NBO could obviously be implemented earlier in the clinical setting. Therefore, our present experiments were designed to account for a 60 min delay of treatment initiation of HBO relative to NBO. NBO was started 30 min after MCAO because this time was effective in one recent study [22] and appears to be the realistic minimum interval that can be achieved in most outpatient treatment situations. NBO was administered for a 5 h period because prolonged treatment was most effective in a well-designed study by Flynn and Auer [6] and in another study using a permanent focal ischemia model [11]. Nevertheless, NBO failed to reduce infarct size and neurological deficit compared to air treated rats in our experiments in contrast to previous reports by other groups [6,11,12,22,23]. A potential explanation for this discrepancy could be the longer MCA occlusion period in our experiments. In this setting, the 30 min time interval until treatment initiation may have been too long as the time from onset of ischemia to initiation of oxygen therapy is of great importance [14,30]. Alternatively, prolonged exposure to NBO for 5 h may have increased production of reactive oxygen species, although recent studies did not find any evidence for enhanced oxygen radical induced cell damage after NBO treatment [15,20,24]. Exposure to normobaric oxygen in these studies, however, was shorter than in our study and did not include the reperfusion period during which oxygen-radical induced damage is of particular importance. Also, rats were anaesthesized only during surgical procedures in our experiments in contrast to previous studies. As inhalative narcotics can alter brain metabolism and infarct size [8] this may offer a further explanation for outcome differences between the studies. Results from clinical studies on hyperoxia in stroke patients are controversial. Ronning and Guldvog [18] observed a worse 1-year-outcome in stroke patients receiving supplementary oxygen. While in this study patients were enrolled in a time window of 24 h, Singhal et al. [21] found an improved clinical outcome and less MRI abnormalities when normobaric hyperoxia was started within 12 h after stroke-onset.

The sequential administration of normobaric and hyperbaric oxygen therapy may be an attractive option in the clinical stroke setting because it combines the advantages of early application of NBO with the apparently more powerful but logistically challenging protective effect of delayed HBO. To our knowledge, this concept so far has only been studied in a study of permanent cortical murine ischemia from our group [27]. Similar to that study, administering NBO prior to HBO resulted in no benefit beyond protection by delayed HBO alone in the present study. However, this hypothesis may have to be retested using a shorter time window than 30 min for NBO.

In conclusion, our findings are of relevance for the potential translation of oxygen therapy from experimental into clinical ischemic stroke because they suggest a more powerful protective effect of HBO than of NBO even when accounting for variables such as delay of treatment-onset and prolonged treatment duration.

Acknowledgments

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Quantification of Neurocognitive Changes Before, During, and After Hyperbaric Oxygen Therapy in a Case of Fetal Alcohol Syndrome

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ABSTRACT. Fetal alcohol syndrome (FAS) is the most common nonhereditary cause of mental retardation, with deficits in general intellectual functioning, learning, memory, attention, and problem-solving. Presented here is the first case in which measured neurocognitive abilities were determined before, during, and after hyperbaric oxygen therapy in a case of FAS involving a teenage male patient. Memory, reaction time, and visual motor speed assessments were compared. After 40 hyperbaric treatments with 100% oxygen at 1.5 atmospheres absolute, the patient's performance in 6 of 6 categories of the computer-administered test battery improved. Word composite (verbal) scores improved from 55% to 73%, memory composite (visual) scores improved from 38% to 55%, reaction time composites improved from 1.03 to 0.53 seconds, impulse control composite scores improved from 8 to 5, and visual motor speed scores improved from 18.6 to 19.03. The patient's subjective symptoms diminished 94%. Six months after these treatments, the patient's verbal memory was maintained at 73% without any other interventions; impulsivity continued to improve, whereas other indices did not. Thirty-three additional treatments continued to improve test performance, with verbal memory at 95%, visual memory at 57%, and a 100% reduction of subjective symptoms. This patient, with 15-year-matured FAS, benefited from a short course of low-pressure hyperbaric oxygen therapy, sustained durable cognitive improvements, and continued to exhibit improvement with another short course of treatments. *Pediatrics* **2005;116:e586–e591. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2851;** ***hyperbaric oxygen therapy, fetal alcohol syndrome.***

ABBREVIATIONS. FAS, fetal alcohol syndrome; ATA, atmospheres absolute; HBOT, hyperbaric oxygen therapy; ARND, alcohol-related neurodevelopmental disorders; DCS, decompression sickness; SPECT, single-photon emission computed tomographic.

Fetal alcohol syndrome (FAS) and alcohol-related neurodevelopmental disorders (ARND) are the leading causes of nonhereditary mental retardation. FAS is caused by maternal consumption of alcohol during pregnancy, with growth deficiencies and a characteristic set of minor facial traits that tend to become more transparent as the child matures. In addition to deficits in general intellectual functioning, individuals with FAS/ARND often demonstrate difficulties with learning, memory, attention, and problem-solving skills, as well as mental and social impairments. Children with ARND do not have the characteristic facial defects and growth deficiencies. The prevalence of FAS in the general population of the United States is thought to be between 0.5 and 2 cases per 1000 births, and the prevalence of FAS and alcohol-related birth defects combined is at least 10 cases per 1000 births, or 1% of all births.[1] Fetal alcohol spectrum disorders is now the accepted general term describing the range of effects that can occur among individuals whose mothers drank alcohol during pregnancy. Other than supportive services, there is no treatment; according to the Centers for Disease Control and Prevention, FAS is considered irreversible and incurable.

It has been a decade since Harch et al[2] first used hyperbaric oxygen therapy (HBOT) for a child with a neurodevelopmental disorder in North America, after making the observation that patients with neurologic conditions who were treated with standard HBOT for chronic wound problems experienced improvement in their neurologic problems. Several years earlier, Neubauer et al[3–5] reported several cases of single-photon emission computed tomographic (SPECT) brain imaging before and after HBOT for stroke, near drowning, and natural gas poisoning, with recovery of neurologic function. Subsequently, Harch et al[2,6,7] performed the same sequence of SPECT scans/HBOT/SPECT scans for commercial divers with brain decompression sickness (DCS) and obtained results similar to those of Neubauer et al[3–5] for patients with acute, subacute, or chronic carbon monoxide poisoning, patients with acute, subacute, or chronic brain DCS, and patients with chronic ischemic, hypoxic, traumatic, and/or hypoxic brain injuries.

Commercial divers with DCS of the brain or spinal cord were flown in comatose and/or paralyzed condition from the oil and gas fields of the Gulf of Mexico. These injured divers showed neurologic improvement far exceeding published reports and current expectations. The notable improvement was attributable to a protocol that treated beyond the medical standard of a few HBOT treatments. Some patients required as many as 100 treatments before reaching a clinical plateau. Minutes to hours after the onset of DCS, tissue damage continues to develop

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because of persistent occlusion of blood vessels by bubbles or secondary damage to blood vessels caused by passage of bubbles. This situation is virtually identical to the pathologic processes that occur in the brains of people during and after a stroke. Although not widely known or used, HBOT is now considered an important stroke treatment strategy and proved successful in several animal and human stroke studies.[8] The journal *Stroke* published a double-blind study showing that stroke patients who had received HBOT had less disability and better neurologic function 1 year later than those who did not receive HBOT.[9]

Treatment of acute focal cerebral ischemia with HBOT has been reported for animals and humans. In general, the results of research in animals have suggested a promising role for HBOT. Hundreds of cases of human ischemic stroke treated with HBOT have been reported. In approximately one half of the cases, improvement in status was claimed on clinical or electroencephalographic grounds.[10]

It seems that HBOT may play a role in the repair or reconstruction of injured lower motor neurons as well.[11] On the basis of the available literature, it has been suggested that HBOT may provide an effective strategy for the prevention and treatment of numerous neurologic handicaps that plague many children.[12] The senior clinicians involved in the largest randomized trial of HBOT for children with cerebral palsy,[13,14] as well as the McGill pilot study,[15] have been unequivocal regarding the benefits of HBOT for children with brain injuries.[16]

I adapted successfully[17] a computerized neuropsychologic test battery, which was developed originally to evaluate sports concussions at the Center for Sports Medicine Sports Concussion Program of the University of Pittsburgh Medical Center,[18,19] to evaluate victims of carbon monoxide poisoning before and after HBOT. The software evaluates and documents multiple aspects of neurocognitive functioning, including memory, brain processing speed, reaction time, and postconcussive symptoms. Furthermore, unlike standard neurocognitive testing modalities, ImPACT (Immediate Postconcussion Assessment and Cognitive Testing) has shown itself to be a reliable evaluation tool with virtually no practice effect influence on score stability.[20] This computerized evaluation was administered in this first documented case of HBOT for a child with FAS.

CASE REPORT

The child was found abandoned in a train station in Rustov, Russia, as a toddler and subsequently was adopted and brought to the United States. When the patient entered school, numerous problems arose that led eventually to the diagnosis of FAS (category II, because the patient was without confirmed maternal alcohol exposure). Although the patient's exact age was not known, his legal birth date made him 15 years of age at the time of the evaluation, in which he still exhibited several key features of FAS, including classic facial anomalies and neurodevelopmental abnormalities of the central nervous system. Furthermore, it is of interest that, because of his neurocognitive state, the patient was found incompetent to stand trial for an alleged offense in the court system in New Mexico.

The patient was given the aforementioned, computer-administered, test battery, which consists of 7 individual test modules that measure aspects of cognitive functioning including attention, memory, reaction time, and processing speed (Table 1). He took a baseline test, a test midway through his HBOT, and a retest as he completed his initial block of HBOT at treatment 40. The patient was retested 6 months after HBOT and again after completing another 33 treatments.

On the basis of normative data for his age, the patient's baseline scores placed him in the impaired range (Figs 1–5; Table 2). The patient was treated with low-pressure HBOT 5 days per week, for 60 minutes at depth for each treatment (100% oxygen at 1.5 atmospheres absolute [ATA], which is equivalent to the pressure at 17 feet of seawater), in a multiplace chamber with a hood to administer the oxygen. After his 20th treatment, he was retested and demonstrated a precipitous decrease in reaction time and the beginnings of improvement in memory. As is often the case when reaction time improves, impulsivity scores increased initially. By the end of treatment, 5 of 5 composite scores of neurocognitive function showed improvement, although the patient's verbal and visual memory scores still placed him in the borderline impaired range. Impulsivity control and reaction time surpassed the high school mean, and subjective symptoms reported during the evaluation decreased 94% from baseline values.

After 6 months with no additional treatments or interventions of any kind, the patient was retested. His verbal memory score was maintained at 73%. His impulse control composite score continued to improve by decreasing to only 2; however, his visual memory score decreased and was only 13% better than the baseline value. His reaction time was still 36% better than the baseline value but was >0.1 second worse than his 40-treatment exit score of 0.53 second. The patient reentered treatment and, after 33 additional exposures to HBOT, his verbal memory was 95% (pretreatment: 55%), visual memory was 57% (pretreatment: 38%), reaction time was 0.64 second (pretreatment: 1.03 second), visual motor speed score was 20.1 (pretreatment: 18.6), and all previously reported symptoms resolved.

DISCUSSION

In 1992, Rockswold et al[21] reported a study of acute traumatic brain injury. Conducted from 1983 to 1989, the study enrolled 168 patients with Glasgow Coma Scale scores of ≤9. The overall mortality rate was reduced significantly, by 50%, in the HBOT group (57% in the group with increased intracranial pressure). In 2001, Rockswold et al[22] reported that HBOT improved the cerebral metabolic rate for oxygen, decreased cerebrospinal fluid lactate levels (a marker of damaged brain cells), and reduced intracranial pressure. Those authors showed the ability of

TABLE 1. Neuropsychologic Test Modules

Test Module	Ability Area
Word discrimination	Attentional processes, verbal recognition
Symbol memory	Visual working memory, visual processing speed
Sequential digit tracking	Sustained attention, reaction time
Visual span	Visual attention, immediate memory
Symbol matching	Visual processing speed, learning and memory
Color click	Focused attention, response inhibition, reaction time
Three letters	Working memory, visual motor response speed

Results from these tests are computed into overall memory, reaction time, and processing speed composite scores (normative data are available at www.impacttest.com).

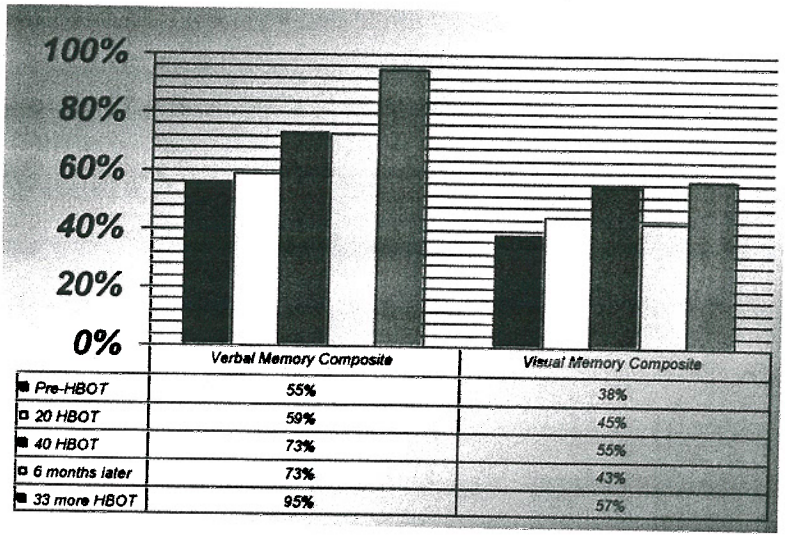

Fig 1. Changes in verbal and visual memory composite scores over the course of HBOT. The high school means were 87.49% (SD: 9%) for verbal memory and 77.89% (SD: 13.16%) for visual memory.

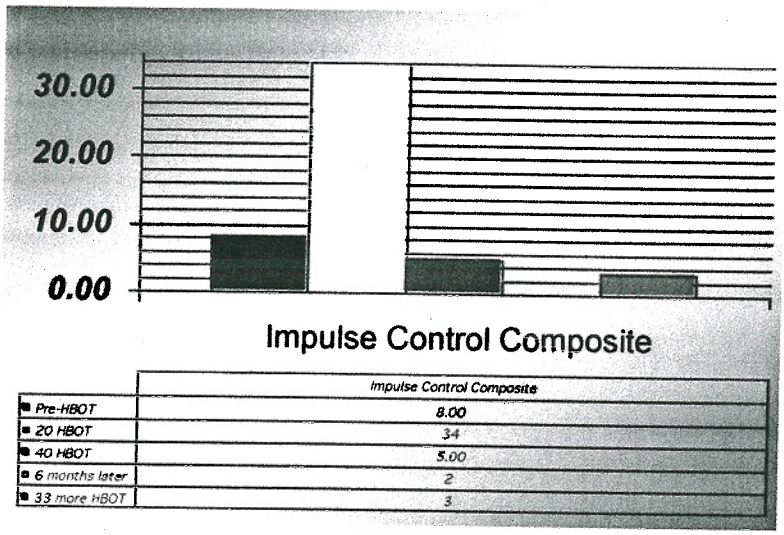

Fig 2. Impulse control composite scores. With a rapid decrease and improvement in reaction time, there is a tendency for impulsivity scores to initially increase, as shown halfway through the first treatment series, but the exit score represents a 38% improvement from the baseline value and is better than the high school mean of 9.51 (SD: 8.68).

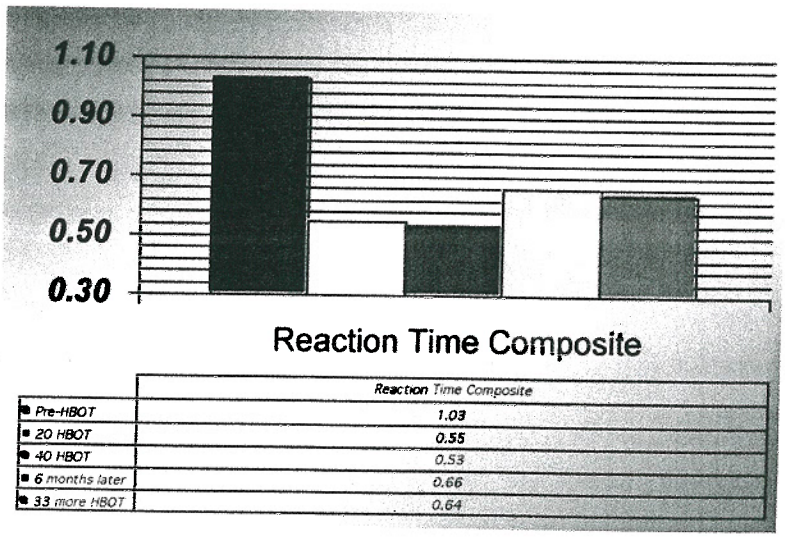

Fig 3. Reaction time composite. Reaction time improvement bettered the high school mean of 0.565 seconds (SD: 0.08 seconds) after 40 treatments.

HBOT to recouple blood flow with metabolism. This is relevant because it is time to revise the old concept that brain injury is a condition for which there is no treatment other than supportive measures.

Furthermore, the axiom that old injuries are static or irreversible is untenable. It is now recognized in neurology that deterioration attributable to brain damage at birth may take place over 28 years.[23] This

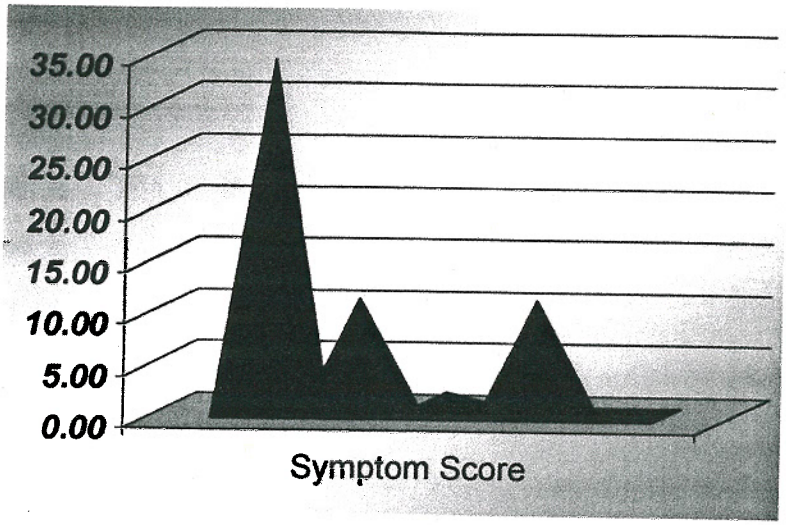

Fig 4. Symptom scores. The computer-administered evaluation asks patients to score subjective symptoms relevant to brain injury that they may be having. The decrease in reported symptoms is consistent with the global improvement this patient displayed in the other modules of the test. The return of some symptoms after 6 months is also consistent with the partial deterioration in some of his scores, but the score decreased to 0 with additional HBOT.

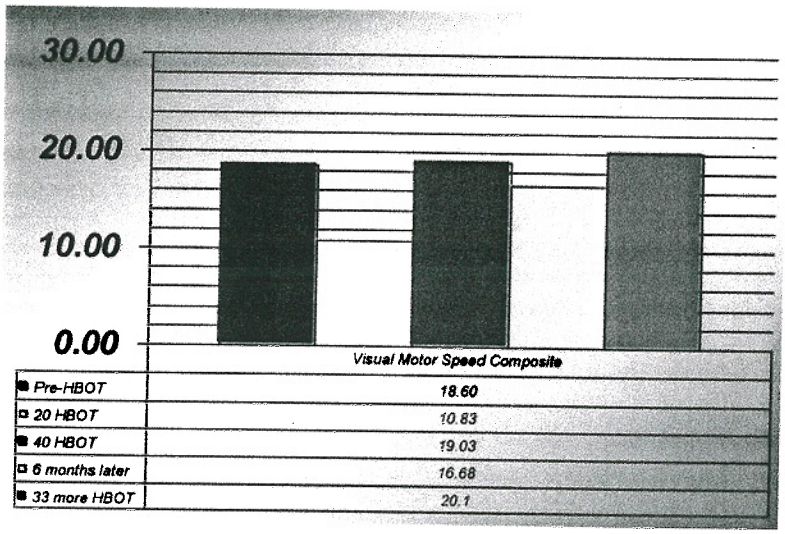

Fig 5. Visual motor speed composite score. Visual motor speed improved with treatment but remained in the borderline impaired range (high school mean: 36.81).

mirrors the adult situation.[24] Furthermore, stem or progenitor cells have been found in the adult brain in the past decade, and they can result in neural regeneration.[25] This recovery process is oxygen dependent and, on first principles, is much more likely to take place in a youngster than in an adult. There is now conclusive evidence from altitude studies that the capillary density can be increased even in the adult mammalian brain.[26]

However, there is trepidation in using extra oxygen to treat children with neurologic problems, because of ingrained concern regarding retinopathy. Tissue hypoxia is compounded by the intravascular sequestration of leukocytes, which release oxygen free radicals. These mechanisms, which constitute the inflammatory response, seem to be activated inappropriately in reperfusion injury and are stimulated by hypoxic signaling produced by increased levels of hypoxia-inducible factor 1α,[27] which also upregulates the production of vascular endothelial growth factor. Therefore, it seems to be hypoxia, created by abrupt reduction of incubator oxygen levels, and not oxygen toxicity that is responsible for neovascularization in retinopathy of prematurity.[28,29]

The computer assessment used in this case seems to be a very useful tool for monitoring changes in neurocognitive function after a brain injury and has application beyond the evaluation of sports-related concussions. HBOT may be useful in the treatment of neurologic injury even if applied in the nonacute period,[30,31] as it was with this patient. Patients with DCS sometimes needed to be treated 100 times before a clinical plateau was reached, and the block of 33 additional treatments continued to improve this patient's neurocognitive function when given at a later date (7 months after the end of his first block of treatments). On the basis of previous experience with DCS cases, this patient might have maintained some of his gains better if he had received additional treatments in the 6-month period after his initial treatment ended, as the continued improvement in his neurocognitive test results with resumption of therapy 7 months later indicates. No conclusion should be drawn from this case regarding how to use HBOT to treat a newborn with evidence of fetal alcohol exposure, because the pathologic features of a more acute exposure to alcohol may not be like those of an old exposure. The lack of appreciation of the pathologic differences in acute versus chronic brain inju-

TABLE 2. Scoring Generated by Computer Assessment of Neurocognitive Function

ImPACT Clinical Report	Before HBOT	After 20 HBOT Treatments	After 40 HBOT Treatments	6 mo Later	After 33 More HBOT Treatments, 73 Total
Examination language	English	English	English	English	English
Word memory					
Hits (immediate), no.	10	11	12	12	11
Correct distractors (immediate), no.	11	12	12	12	10
Learning correct, %	88	96	100	100	86
Hits (delay), no.	10	11	11	11	9
Correct distractors (delay), no.	12	12	12	11	11
Delayed memory correct, %	92	96	96	92	83
Total correct, %	90	96	98	96	85
Design memory					
Hits (immediate), no.	8	9	8	7	6
Correct distractors (immediate), no.	4	6	6	8	6
Learning correct, %	50	63	58	63	50
Hits (delay), no.	9	7	7	4	6
Correct distractors (delay), no.	7	5	8	10	9
Delayed memory correct, %	67	50	63	58	63
Total correct, %	58	56	60	60	56
X's & O's					
Total correct (memory), no.	2	4	6	3	7
Total correct (interference), no.	72	41	85	71	72
Average correct reaction time (interference), s	0.84	0.84	0.81	1.16	1.13
Total incorrect (interference), no.	8	34	5	2	2
Average incorrect reaction time (interference), s	1.57	1.28	0.58	1.75	0.43
Symbol match					
Total correct (symbols), no.	27	26	27	27	26
Average correct reaction time (symbols), s	2.06	2.46	2.36	2.46	2.36
Total correct (symbols hidden), no.	2	0	2	2	9
Average correct reaction time (symbols hidden), s	1.70	0.00	2.23	6.24	3.95
Color match					
Total correct, no.	1	0	0	0	0
Average correct reaction time, s	1.55	0.00	0.00	0.00	0.00
Total commissions, no.	0	0	0	0	1
Average commissions reaction time, s	0.00	0.00	0.00	0.00	1.41
Three letters					
Total correct, no.	2	4	5	5	5
Average correct reaction time, s	8	12	15	15	15
Total letters correct, %	53	80	100	100	100
Average time to first click, s	3.44	4.08	4.33	4.57	3.84
Average counted, no.	6.4	5.6	6.4	5.2	8
Average counted correctly, no.	6.4	3.8	5.6	5.2	7.4
Composite scores					
Memory composite (verbal), %	55	59	73	73	95
Memory composite (visual), %	38	45	55	43	57
Visual motor speed composite score	1.03	0.55	0.53	16.68	20.10
Impulse control composite score	8	34	5	2	3

ries and how to treat such injuries has produced a legacy of equivocal results. Dosage matters with HBOT, especially in treating chronic brain injuries. Pressures used for treatment of diabetic foot ulcers (2.4 ATA) or acute DCS (2.8 ATA) probably will not produce the desired healing of mature brain injuries.

In any situation in which application of appropriate measurements gives concrete evidence of changes induced by treatment, the significance of limited numbers of patients is increased. In a sense, this FAS patient acted as his own control, which was facilitated by the level of documentation that the computer-generated neurocognitive evaluation was able to provide. Low-pressure HBOT is a therapy with an extremely low risk profile and relatively low cost, with potential benefits that seem to be significant and measurable for a condition considered incurable, with no treatment at our disposal. In this case, a youth with 15-year-matured FAS benefited from a short course of low-pressure HBOT and sustained durable cognitive improvements. Given the implications, these results should receive consideration for broader study as soon as possible.

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Quantification of Neurocognitive Changes Before, During, and After Hyperbaric Oxygen Therapy in a Case of Fetal Alcohol Syndrome

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Quantification of Neurocognitive Changes Before, During, and After Hyperbaric Oxygen Therapy in a Case of Fetal Alcohol Syndrome

Kenneth P. Stoller, MD

ABSTRACT. Fetal alcohol syndrome (FAS) is the most common nonhereditary cause of mental retardation, with deficits in general intellectual functioning, learning, memory, attention, and problem-solving. Presented here is the first case in which measured neurocognitive abilities were determined before, during, and after hyperbaric oxygen therapy in a case of FAS involving a teenage male patient. Memory, reaction time, and visual motor speed assessments were compared. After 40 hyperbaric treatments with 100% oxygen at 1.5 atmospheres absolute, the patient's performance in 6 of 6 categories of the computer-administered test battery improved. Word composite (verbal) scores improved from 55% to 73%, memory composite (visual) scores improved from 38% to 55%, reaction time composites improved from 1.03 to 0.53 seconds, impulse control composite scores improved from 8 to 5, and visual motor speed scores improved from 18.6 to 19.03. The patient's subjective symptoms diminished 94%. Six months after these treatments, the patient's verbal memory was maintained at 73% without any other interventions; impulsivity continued to improve, whereas other indices did not. Thirty-three additional treatments continued to improve test performance, with verbal memory at 95%, visual memory at 57%, and a 100% reduction of subjective symptoms. This patient, with 15-year-matured FAS, benefited from a short course of low-pressure hyperbaric oxygen therapy, sustained durable cognitive improvements, and continued to exhibit improvement with another short course of treatments. *Pediatrics* **2005;116:e586–e591. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2851;** ***hyperbaric oxygen therapy, fetal alcohol syndrome.***

ABBREVIATIONS. FAS, fetal alcohol syndrome; ATA, atmospheres absolute; HBOT, hyperbaric oxygen therapy; ARND, alcohol-related neurodevelopmental disorders; DCS, decompression sickness; SPECT, single-photon emission computed tomographic.

Fetal alcohol syndrome (FAS) and alcohol-related neurodevelopmental disorders (ARND) are the leading causes of nonhereditary mental retardation. FAS is caused by maternal consumption of alcohol during pregnancy, with growth deficiencies and a characteristic set of minor facial traits that tend to become more transparent as the child matures. In addition to deficits in general intellectual functioning, individuals with FAS/ARND often demonstrate difficulties with learning, memory, attention, and problem-solving skills, as well as mental and social impairments. Children with ARND do not have the characteristic facial defects and growth deficiencies. The prevalence of FAS in the general population of the United States is thought to be between 0.5 and 2 cases per 1000 births, and the prevalence of FAS and alcohol-related birth defects combined is at least 10 cases per 1000 births, or 1% of all births.[1] Fetal alcohol spectrum disorders is now the accepted general term describing the range of effects that can occur among individuals whose mothers drank alcohol during pregnancy. Other than supportive services, there is no treatment; according to the Centers for Disease Control and Prevention, FAS is considered irreversible and incurable.

It has been a decade since Harch et al[2] first used hyperbaric oxygen therapy (HBOT) for a child with a neurodevelopmental disorder in North America, after making the observation that patients with neurologic conditions who were treated with standard HBOT for chronic wound problems experienced improvement in their neurologic problems. Several years earlier, Neubauer et al[3–5] reported several cases of single-photon emission computed tomographic (SPECT) brain imaging before and after HBOT for stroke, near drowning, and natural gas poisoning, with recovery of neurologic function. Subsequently, Harch et al[2,6,7] performed the same sequence of SPECT scans/HBOT/SPECT scans for commercial divers with brain decompression sickness (DCS) and obtained results similar to those of Neubauer et al[3–5] for patients with acute, subacute, or chronic carbon monoxide poisoning, patients with acute, subacute, or chronic brain DCS, and patients with chronic ischemic, hypoxic, traumatic, and/or hypoxic brain injuries.

Commercial divers with DCS of the brain or spinal cord were flown in comatose and/or paralyzed condition from the oil and gas fields of the Gulf of Mexico. These injured divers showed neurologic improvement far exceeding published reports and current expectations. The notable improvement was attributable to a protocol that treated beyond the medical standard of a few HBOT treatments. Some patients required as many as 100 treatments before reaching a clinical plateau. Minutes to hours after the onset of DCS, tissue damage continues to develop

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because of persistent occlusion of blood vessels by bubbles or secondary damage to blood vessels caused by passage of bubbles. This situation is virtually identical to the pathologic processes that occur in the brains of people during and after a stroke. Although not widely known or used, HBOT is now considered an important stroke treatment strategy and proved successful in several animal and human stroke studies.[8] The journal *Stroke* published a double-blind study showing that stroke patients who had received HBOT had less disability and better neurologic function 1 year later than those who did not receive HBOT.[9]

Treatment of acute focal cerebral ischemia with HBOT has been reported for animals and humans. In general, the results of research in animals have suggested a promising role for HBOT. Hundreds of cases of human ischemic stroke treated with HBOT have been reported. In approximately one half of the cases, improvement in status was claimed on clinical or electroencephalographic grounds.[10]

It seems that HBOT may play a role in the repair or reconstruction of injured lower motor neurons as well.[11] On the basis of the available literature, it has been suggested that HBOT may provide an effective strategy for the prevention and treatment of numerous neurologic handicaps that plague many children.[12] The senior clinicians involved in the largest randomized trial of HBOT for children with cerebral palsy,[13,14] as well as the McGill pilot study,[15] have been unequivocal regarding the benefits of HBOT for children with brain injuries.[16]

I adapted successfully[17] a computerized neuropsychologic test battery, which was developed originally to evaluate sports concussions at the Center for Sports Medicine Sports Concussion Program of the University of Pittsburgh Medical Center,[18,19] to evaluate victims of carbon monoxide poisoning before and after HBOT. The software evaluates and documents multiple aspects of neurocognitive functioning, including memory, brain processing speed, reaction time, and postconcussive symptoms. Furthermore, unlike standard neurocognitive testing modalities, ImPACT (Immediate Postconcussion Assessment and Cognitive Testing) has shown itself to be a reliable evaluation tool with virtually no practice effect influence on score stability.[20] This computerized evaluation was administered in this first documented case of HBOT for a child with FAS.

CASE REPORT

The child was found abandoned in a train station in Rustov, Russia, as a toddler and subsequently was adopted and brought to the United States. When the patient entered school, numerous problems arose that led eventually to the diagnosis of FAS (category II, because the patient was without confirmed maternal alcohol exposure). Although the patient's exact age was not known, his legal birth date made him 15 years of age at the time of the evaluation, in which he still exhibited several key features of FAS, including classic facial anomalies and neurodevelopmental abnormalities of the central nervous system. Furthermore, it is of interest that, because of his neurocognitive state, the patient was found incompetent to stand trial for an alleged offense in the court system in New Mexico.

The patient was given the aforementioned, computer-administered, test battery, which consists of 7 individual test modules that measure aspects of cognitive functioning including attention, memory, reaction time, and processing speed (Table 1). He took a baseline test, a test midway through his HBOT, and a retest as he completed his initial block of HBOT at treatment 40. The patient was retested 6 months after HBOT and again after completing another 33 treatments.

On the basis of normative data for his age, the patient's baseline scores placed him in the impaired range (Figs 1–5; Table 2). The patient was treated with low-pressure HBOT 5 days per week, for 60 minutes at depth for each treatment (100% oxygen at 1.5 atmospheres absolute [ATA], which is equivalent to the pressure at 17 feet of seawater), in a multiplace chamber with a hood to administer the oxygen. After his 20th treatment, he was retested and demonstrated a precipitous decrease in reaction time and the beginnings of improvement in memory. As is often the case when reaction time improves, impulsivity scores increased initially. By the end of treatment, 5 of 5 composite scores of neurocognitive function showed improvement, although the patient's verbal and visual memory scores still placed him in the borderline impaired range. Impulsivity control and reaction time surpassed the high school mean, and subjective symptoms reported during the evaluation decreased 94% from baseline values.

After 6 months with no additional treatments or interventions of any kind, the patient was retested. His verbal memory score was maintained at 73%. His impulse control composite score continued to improve by decreasing to only 2; however, his visual memory score decreased and was only 13% better than the baseline value. His reaction time was still 36% better than the baseline value but was >0.1 second worse than his 40-treatment exit score of 0.53 second. The patient reentered treatment and, after 33 additional exposures to HBOT, his verbal memory was 95% (pretreatment: 55%), visual memory was 57% (pretreatment: 38%), reaction time was 0.64 second (pretreatment: 1.03 second), visual motor speed score was 20.1 (pretreatment: 18.6), and all previously reported symptoms resolved.

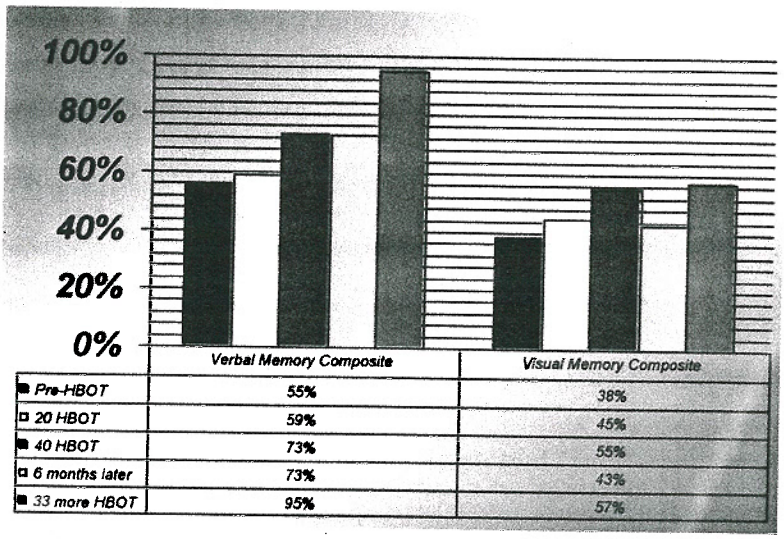
DISCUSSION

In 1992, Rockswold et al[21] reported a study of acute traumatic brain injury. Conducted from 1983 to 1989, the study enrolled 168 patients with Glasgow Coma Scale scores of ≤9. The overall mortality rate was reduced significantly, by 50%, in the HBOT group (57% in the group with increased intracranial pressure). In 2001, Rockswold et al[22] reported that HBOT improved the cerebral metabolic rate for oxygen, decreased cerebrospinal fluid lactate levels (a marker of damaged brain cells), and reduced intracranial pressure. Those authors showed the ability of

TABLE 1. Neuropsychologic Test Modules

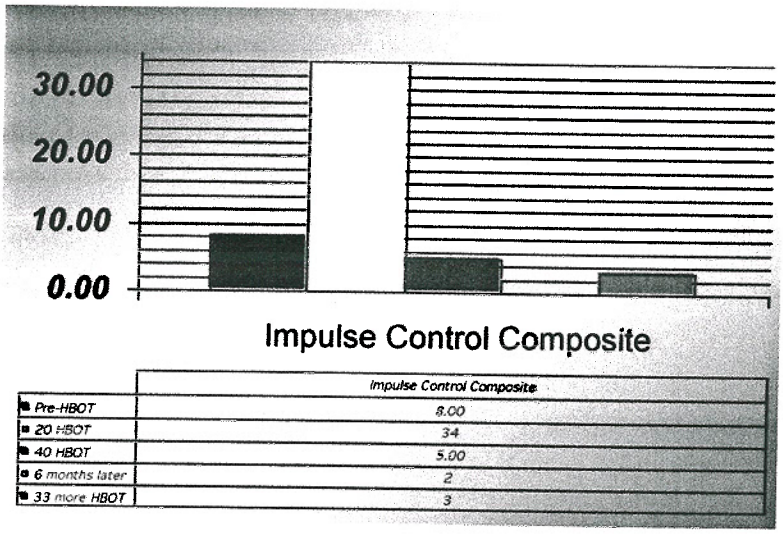
Test Module	Ability Area
Word discrimination	Attentional processes, verbal recognition
Symbol memory	Visual working memory, visual processing speed
Sequential digit tracking	Sustained attention, reaction time
Visual span	Visual attention, immediate memory
Symbol matching	Visual processing speed, learning and memory
Color click	Focused attention, response inhibition, reaction time
Three letters	Working memory, visual motor response speed

Results from these tests are computed into overall memory, reaction time, and processing speed composite scores (normative data are available at www.impacttest.com).



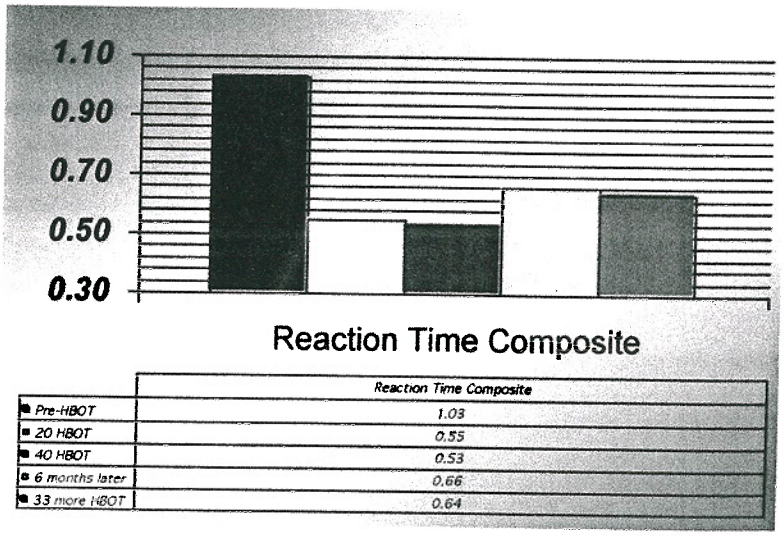
	Verbal Memory Composite	Visual Memory Composite
Pre-HBOT	55%	38%
20 HBOT	59%	45%
40 HBOT	73%	55%
6 months later	73%	43%
33 more HBOT	95%	57%

Fig 1. Changes in verbal and visual memory composite scores over the course of HBOT. The high school means were 87.49% (SD: 9%) for verbal memory and 77.89% (SD: 13.16%) for visual memory.



	Impulse Control Composite
Pre-HBOT	8.00
20 HBOT	34
40 HBOT	5.00
6 months later	2
33 more HBOT	3

Fig 2. Impulse control composite scores. With a rapid decrease and improvement in reaction time, there is a tendency for impulsivity scores to initially increase, as shown halfway through the first treatment series, but the exit score represents a 38% improvement from the baseline value and is better than the high school mean of 9.51 (SD: 8.68).



	Reaction Time Composite
Pre-HBOT	1.03
20 HBOT	0.55
40 HBOT	0.53
6 months later	0.66
33 more HBOT	0.64

Fig 3. Reaction time composite. Reaction time improvement bettered the high school mean of 0.565 seconds (SD: 0.08 seconds) after 40 treatments.

HBOT to recouple blood flow with metabolism. This is relevant because it is time to revise the old concept that brain injury is a condition for which there is no treatment other than supportive measures.

Furthermore, the axiom that old injuries are static or irreversible is untenable. It is now recognized in neurology that deterioration attributable to brain damage at birth may take place over 28 years.[23] This

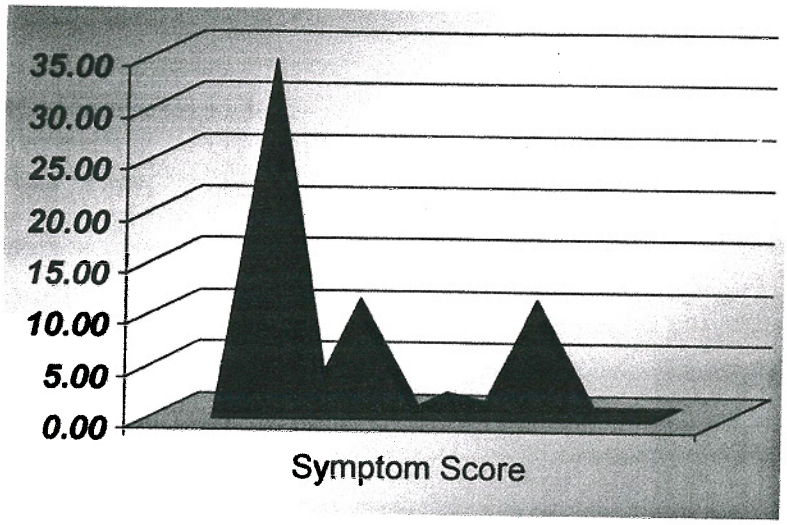


Fig 4. Symptom scores. The computer-administered evaluation asks patients to score subjective symptoms relevant to brain injury that they may be having. The decrease in reported symptoms is consistent with the global improvement this patient displayed in the other modules of the test. The return of some symptoms after 6 months is also consistent with the partial deterioration in some of his scores, but the score decreased to 0 with additional HBOT.

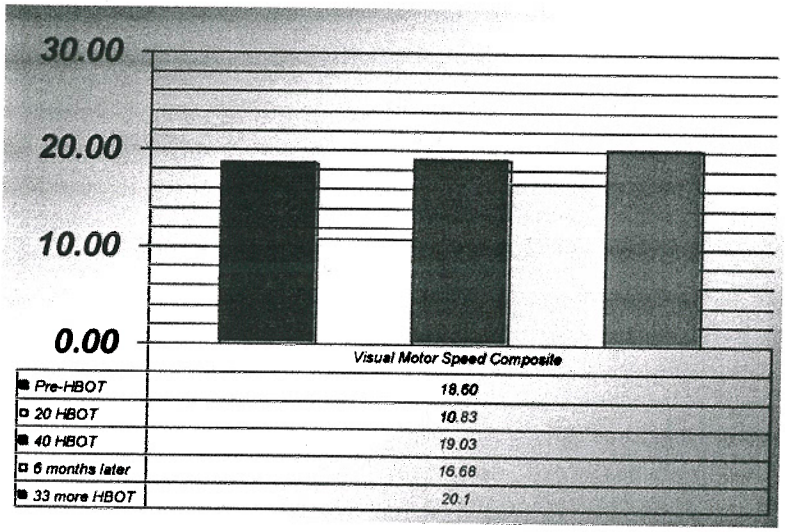


Fig 5. Visual motor speed composite score. Visual motor speed improved with treatment but remained in the borderline impaired range (high school mean: 36.81).

mirrors the adult situation.[24] Furthermore, stem or progenitor cells have been found in the adult brain in the past decade, and they can result in neural regeneration.[25] This recovery process is oxygen dependent and, on first principles, is much more likely to take place in a youngster than in an adult. There is now conclusive evidence from altitude studies that the capillary density can be increased even in the adult mammalian brain.[26]

However, there is trepidation in using extra oxygen to treat children with neurologic problems, because of ingrained concern regarding retinopathy. Tissue hypoxia is compounded by the intravascular sequestration of leukocytes, which release oxygen free radicals. These mechanisms, which constitute the inflammatory response, seem to be activated inappropriately in reperfusion injury and are stimulated by hypoxic signaling produced by increased levels of hypoxia-inducible factor 1α,[27] which also upregulates the production of vascular endothelial growth factor. Therefore, it seems to be hypoxia, created by abrupt reduction of incubator oxygen levels, and not oxygen toxicity that is responsible for neovascularization in retinopathy of prematurity.[28,29]

The computer assessment used in this case seems to be a very useful tool for monitoring changes in neurocognitive function after a brain injury and has application beyond the evaluation of sports-related concussions. HBOT may be useful in the treatment of neurologic injury even if applied in the nonacute period,[30,31] as it was with this patient. Patients with DCS sometimes needed to be treated 100 times before a clinical plateau was reached, and the block of 33 additional treatments continued to improve this patient's neurocognitive function when given at a later date (7 months after the end of his first block of treatments). On the basis of previous experience with DCS cases, this patient might have maintained some of his gains better if he had received additional treatments in the 6-month period after his initial treatment ended, as the continued improvement in his neurocognitive test results with resumption of therapy 7 months later indicates. No conclusion should be drawn from this case regarding how to use HBOT to treat a newborn with evidence of fetal alcohol exposure, because the pathologic features of a more acute exposure to alcohol may not be like those of an old exposure. The lack of appreciation of the pathologic differences in acute versus chronic brain inju-

TABLE 2. Scoring Generated by Computer Assessment of Neurocognitive Function

ImPACT Clinical Report	Before HBOT	After 20 HBOT Treatments	After 40 HBOT Treatments	6 mo Later	After 33 More HBOT Treatments, 73 Total
Examination language	English	English	English	English	English
Word memory					
Hits (immediate), no.	10	11	12	12	11
Correct distractors (immediate), no.	11	12	12	12	10
Learning correct, %	88	96	100	100	86
Hits (delay), no.	10	11	11	11	9
Correct distractors (delay), no.	12	12	12	11	11
Delayed memory correct, %	92	96	96	92	83
Total correct, %	90	96	98	96	85
Design memory					
Hits (immediate), no.	8	9	8	7	6
Correct distractors (immediate), no.	4	6	6	8	6
Learning correct, %	50	63	58	63	50
Hits (delay), no.	9	7	7	4	6
Correct distractors (delay), no.	7	5	8	10	9
Delayed memory correct, %	67	50	63	58	63
Total correct, %	58	56	60	60	56
X's & O's					
Total correct (memory), no.	2	4	6	3	7
Total correct (interference), no.	72	41	85	71	72
Average correct reaction time (interference), s	0.84	0.84	0.81	1.16	1.13
Total incorrect (interference), no.	8	34	5	2	2
Average incorrect reaction time (interference), s	1.57	1.28	0.58	1.75	0.43
Symbol match					
Total correct (symbols), no.	27	26	27	27	26
Average correct reaction time (symbols), s	2.06	2.46	2.36	2.46	2.36
Total correct (symbols hidden), no.	2	0	2	2	9
Average correct reaction time (symbols hidden), s	1.70	0.00	2.23	6.24	3.95
Color match					
Total correct, no.	1	0	0	0	0
Average correct reaction time, s	1.55	0.00	0.00	0.00	0.00
Total commissions, no.	0	0	0	0	1
Average commissions reaction time, s	0.00	0.00	0.00	0.00	1.41
Three letters					
Total correct, no.	2	4	5	5	5
Average correct reaction time, s	8	12	15	15	15
Total letters correct, %	53	80	100	100	100
Average time to first click, s	3.44	4.08	4.33	4.57	3.84
Average counted, no.	6.4	5.6	6.4	5.2	8
Average counted correctly, no.	6.4	3.8	5.6	5.2	7.4
Composite scores					
Memory composite (verbal), %	55	59	73	73	95
Memory composite (visual), %	38	45	55	43	57
Visual motor speed composite score	1.03	0.55	0.53	16.68	20.10
Impulse control composite score	8	34	5	2	3

ries and how to treat such injuries has produced a legacy of equivocal results. Dosage matters with HBOT, especially in treating chronic brain injuries. Pressures used for treatment of diabetic foot ulcers (2.4 ATA) or acute DCS (2.8 ATA) probably will not produce the desired healing of mature brain injuries.

In any situation in which application of appropriate measurements gives concrete evidence of changes induced by treatment, the significance of limited numbers of patients is increased. In a sense, this FAS patient acted as his own control, which was facilitated by the level of documentation that the computer-generated neurocognitive evaluation was able to provide. Low-pressure HBOT is a therapy with an extremely low risk profile and relatively low cost, with potential benefits that seem to be significant and measurable for a condition considered incurable, with no treatment at our disposal. In this case, a youth with 15-year-matured FAS benefited from a short course of low-pressure HBOT and sustained durable cognitive improvements. Given the implications, these results should receive consideration for broader study as soon as possible.

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Quantification of Neurocognitive Changes Before, During, and After Hyperbaric Oxygen Therapy in a Case of Fetal Alcohol Syndrome

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Hyperbaric oxygen in traumatic brain injury

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Objectives: *This critical literature review examines historical and current investigations on the efficacy and mechanisms of hyperbaric oxygen (HBO) treatment in traumatic brain injury (TBI). Potential safety risks and oxygen toxicity, as well as HBO's future potential, are also discussed.*
Methods: *Directed literature review.*
Results: *Historically, cerebral vasoconstriction and increased oxygen availability were seen as the primary mechanisms of HBO in TBI. HBO now appears to be improving cerebral aerobic metabolism at a cellular level, namely, by enhancing damaged mitochondrial recovery. HBO given at the ideal treatment paradigm, 1.5 ATA for 60 minutes, does not appear to produce oxygen toxicity and is relatively safe.*
Discussion: *The use of HBO in TBI remains controversial. Growing evidence, however, shows that HBO may be a potential treatment for patients with severe brain injury. Further investigations, including a multicenter prospective randomized clinical trial, will be required to definitively define the role of HBO in severe TBI.* [Neurol Res 2007; **29**: 162–172]

Keywords: Cerebral metabolism; hyperbaric oxygen; intracranial pressure; traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is called the silent epidemic of the USA. Two million people suffer TBI each year in the USA and approximately one million of them require an emergency room visit; 500,000 are hospitalized and 50,000 die. This results in direct and indirect costs of 56 billion dollars annually to our country[1]. The magnitude of the problem is shown in the statement by Dr Thomas A. Ginnarelli, a neurosurgeon specializing in TBI: 'In the last twelve years, the number of deaths from head injury has exceeded all the military deaths in all the wars [up to the Vietnam War] fought by this nation since 1776'. Various drug and hypothermia multicenter trials have failed to show improvement in functional outcome and mortality rates in patients suffering from TBI[2–5]. In recent years, however, there has been promising animal and clinical research in the area of oxygen (O_2), especially hyperbaric oxygen (HBO), for the treatment of severe TBI[6–10].

The use of HBO in the treatment of TBI has been controversial. Oxygen toxicity and safety concerns have been at the forefront of this controversy. In truth, the complications from HBO have been rare and reversible in the authors' experience. Historically, HBO was seen as a mechanism to decrease cerebral blood flow (CBF) and intracranial pressure (ICP) while increasing O_2 availability to injured brain cells[11–13]. As highly technical equipment has become available in both TBI animal and clinical studies, however, HBO appears to be working at the mitochondrial level to improve cerebral aerobic metabolism after brain injury[7,8,10]. Clinically, HBO has been shown to decrease mortality rates and improve functional outcome in severely brain-injured patients[6,14,15]. As research on HBO continues, the goal is to accomplish a multicenter prospective randomized clinical outcome trial by which the efficacy of HBO in the treatment of severely brain-injured patients is evaluated.

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PATHOPHYSIOLOGY OF TBI

Ischemia has been implicated as a major cause of secondary brain injury and death following severe brain injury[16–18]. Inadequate O_2 supply to the traumatized brain results in the conversion of aerobic metabolism to anaerobic metabolism[19,20]. Anaerobic metabolism results in acidosis and depletion of cellular energy. As the demands for energy production are no longer met, the brain cells lose their ability to maintain ionic homeostasis. Abnormally high intracellular concentrations of calcium occur[21–23]. A combination of cellular acidosis and excessive concentrations of calcium activates various important intracellular proteins. This abnormal cellular environment results in the release of excitatory amino acids and in the formation of highly reactive free radicals that are extremely damaging to cell membranes[24–26]. The high levels of calcium also have been shown to lead to excessive calcium being absorbed on neuronal mitochondria membranes leading to the impairment of mitochondrial respiratory chain-linked oxidative phosphorylation leading to further functional failure of aerobic metabolism[27,28]. Mitochondrial dysfunction can persist for days following the initial insult[29–32].

Paradoxically, during this early phase of injury, metabolic needs of the injured brain tissue are increased

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and CBF and delivery of O_2 in substrate are decreased. This results in what has been termed a 'flow/metabolism mismatch'[27]. Oxygen delivery to brain tissue is impaired not only by decreased CBF but by reduced O_2 diffusion into cells caused by vasogenic and cytotoxic edema. Studies have also shown that local brain tissue oxygen (PtO_2) levels are significantly correlated with ischemia and outcome[33–35]. Van den Brink *et al.* demonstrated the presence of early ischemia at the tissue level with reduced initial PtO_2 and found that low PtO_2 was an independent predictor of death and unfavorable outcome[34].

Many studies indicate that increased cerebrospinal fluid (CSF) lactate product is a marker for this anaerobic metabolism status caused either by a lack of O_2 (ischemia) and/or by damage to the mitochondria[18,19,33,36,37]. A continued high level of lactate in the brain has been shown to be a poor prognostic indicator after brain injury[19,37–39].

The time from the primary brain injury to the occurrence of irreversible cell damage resulting from ischemia and hypoxia varies considerably, depending upon the severity of the injury and the degree of hypoxia[40]. Brain tissue cannot survive without adequate delivery of O_2, and even short periods of O_2 deprivation may result in the activation of pathologic events that contribute to secondary cell damage. Supporting the aerobic processes of the threatened cells could possibly preserve viable, but non-functioning tissue.

HISTORICAL REVIEW OF HBO

The first paper published measuring the effect of HBO on CBF was written by Lambertson *et al.* in 1953[41]. Using the nitrous oxide method developed by Kety and Schmidt, they found a reduction of 24% in the CBF of conscious normal volunteers breathing O_2 at 3.5 atmospheres absolute (ATA) compared to 1 ATA[42]. However, their subjects hyperventilated at increased pressure, resulting in a fall of arterial PCO_2 by 5 mmHg. They concluded that the reduction in CBF was from the arterial hypocapnia.

There were no further published reports on HBO until the following decade. Early in the 1960s, there were two published articles by Illingworth *et al.* and Smith *et al.*, who found that there may be possible therapeutic value to HBO where it gave protection to an ischemic brain shown by electroencephalography[43,44]. However, there was debate whether this protection was negated by the cerebral vasoconstriction found by Lambertson *et al.*[41]. Jacobson *et al.* undertook an experiment measuring CBF and arterial and venous blood gasses with constant arterial PCO_2 in non-injured dogs[45]. They found a 21% reduction in CBF between dogs receiving 100% O_2 at 1 versus 2 ATA. The venous PO_2 remained relatively constant while there were large increases in the arterial PO_2 leading to an increased arterial–venous difference of oxygen ($AVDO_2$). They felt that this increase in the $AVDO_2$ showed that there was a homeostatic mechanism that exists to maintain tissue oxygen levels within fairly close limits and served to mitigate against the deleterious effects of HBO on the central nervous system. Also, because the arterial PCO_2 was held constant, they found that the decrease in CBF was a direct consequence of vasoconstriction. Tindall *et al.* also studied the effect of HBO on CBF in baboons[46]. He did not control arterial PCO_2 and found that there was a drop in CBF as well as arterial PCO_2 during the dive. Their conclusions were similar to that of Lambertson *et al.*[41].

During the mid-1960s, there were reports that the use of HBO may be beneficial in the treatment of cerebral ischemia[47–49]. However, there was one conflicting report by Jacobsen *et al.* that there were larger infarcts in the cerebrum following middle cerebral artery occlusion when HBO was used[50]. Of note was that the number of subjects described in all of these reports was very small.

The first study in which HBO was used to treat experimental TBI was carried out by Dunn *et al.*[51]. The authors exposed dog brains to liquid nitrogen simulating brain contusion. The animals were divided into six groups according to pressure and O_2 received. The mortality for all groups receiving hyperoxia was significantly decreased (15%) in comparison to those that did not (56%). The sizes of the lesions also were reduced in the HBO-treated group, although this finding did not reach statistical significance.

Sukoff *et al.* used two methods to produce cerebral edema in dogs, psyllium seeds and the extradural balloon technique[52]. Both series of dogs were divided into a HBO-treated group (3 ATA for 45 minutes) and a control group. Mortality in the psyllium seed group was 27% for the HBO-treated group and 83% for the control group. In the extradural balloon group, mortality was 50% for the HBO-treated group and 100% for the control group. All surviving HBO-treated dogs were neurologically normal. All animals were killed and their brains showed gross evidence of cerebral edema. However, the HBO-treated brains weighed significantly less than the control brains. They concluded that HBO has a protective effect against experimental cerebral edema.

Sukoff *et al.* published another paper on the effects of HBO on experimental edema[11]. This study was performed again in dogs, using the psyllium seed technique to produce a space occupying lesion. The animals were exposed at 3 ATA for 45 minutes at 8 hours intervals. The results were as follows: mortality rate for the control group was 83% compared to 27% in the HBO-treated group. Cisternal CSF pressure was steadily reduced in the HBO-treated group as compared to the control group which showed steady increase in ICP. They felt that the main action of HBO was at the level of the cerebral blood vessel. HBO caused cerebral vasoconstriction and decreased CBF reducing cerebral edema, yet at the same time, there was increased availability of O_2 at the cellular level. For these reasons, HBO could protect the injured brain against ischemia secondary to cerebral edema.

A similar study was performed by Moody *et al.*, using an extradural balloon in dogs[53]. The 95% mortality rate

in the control group was reduced to 50% by treatment of the dogs with 100% O_2 at 2 ATA for 4 hours following balloon decompression. The quality of survival was good among the survivors of the HBO-treated group. They also concluded that HBO produces better tissue oxygenation during low CBF seen following this type of experimental brain injury.

The next important study on the effect of HBO on CBF was published by Wullenberg *et al.* from Dr Holbach's group in Germany[54]. This study was the first to measure CBF in severely brain-injured patients during HBO treatments. They used thermoprobes to measure the CBF. In contrast to previous published results, they found that CBF increased during the dive during increasing pressures, but once the pressure reached 2.5 ATA, no further rise occurred. During the same time period, blood pressure, pH and arterial PCO_2 remained normal. Arterial PO_2 increased to 1100 mmHg but venous PO_2 increased only slightly. The concentrations of lactate and pyruvate decreased corresponding to the rise in arterial PO_2. The CBF remained slightly elevated after the dive. They concluded that HBO is indicated in cases of severe brain injury.

Mogami *et al.* were one of the first to describe the effect of HBO on ICP in severely brain-injured patients[55]. Sixty-six patients in whom most (51) had TBIs were studied. The HBO treatment was usually given at a pressure of 2 ATA for 1 hour, two times a day; six of these treatments, however, were given at 3 ATA for 30 minutes. In total, 143 treatments were given to the 66 patients. During HBO, 33 patients (50%) showed clinical improvement during the treatment, but usually, regressions occurred after the treatments. CSF pressure was measured during treatment. The pressure was found to decrease during the beginning of treatment, stay at a low level during treatment and then rebound after treatment. The authors also found that lactate/pyruvate ratios were mildly decreased. This was the first published article that challenged that ICP decreases only from vasoconstriction. The group asserted that HBO may be affecting and stabilizing the blood–brain barrier. They also found that TBI has such heterogeneous pathophysiology that HBO may affect individuals differently.

Hayakawa *et al.* demonstrated clinical evidence that HBO treatment decreased CSF pressure[56]. There were two parts in this article, a clinical and experimental portion. The clinical study measured changes in CSF pressure in 13 patients with acute cerebral damage, nine who had TBI and four who underwent craniotomy for a brain tumor. PCO_2 was not controlled or measured. The authors described three main patterns during HBO treatment at 2 ATA for 1 hour: (1) in nine patients, CSF pressure decreased at the beginning of the dive, but rose again at the end; (2) in two patients, CSF pressure fell and remained lower after the dive; (3) in two patients, CSF pressure showed little change with the dive. In the experimental study, HBO was administered to 46 dogs at 3 ATA for 1 hour. Twelve of these dogs underwent extradural balloon technique to produce a brain injury. Both CBF and CSF pressure were measured. The response of the brain-injured dogs to the HBO was variable, but for most part, no or little change in CBF or CSF pressure was seen during and after HBO treatment. The authors concluded that there is considerable variation in the response of CSF pressure to HBO in patients and animals with brain injury, and like Mogami *et al.*, these differences needed to be studied and defined before HBO could be used in the treatment of TBI patients.

During the late 1960s and early 1970s, studies on HBO also were being carried out in Glasgow, Scotland. Miller *et al.* published several experimental animal studies which showed HBO could reduce CBF and ICP by direct cerebral vasoconstriction in injured dogs[57]. In one study, they showed that increased ICP was reduced by 23% by breathing 100% O_2 at normobaric pressures and 37% at 2 ATA in a HBO chamber[57]. The arterial blood pressure and arterial PCO_2 remained constant. They found that ICP was only responsive to HBO when autoregulation was still responsive to carbon dioxide. Another study showed that elevated ICP dropped during HBO treatment (26%), but not as much as with hyperventilation (34%)[13]. However, when HBO was used in conjunction with hyperventilation, an additional 25% drop in ICP was recorded. There was no significant change in CSF lactate in the HBO-treated group. Their conclusion was that HBO caused vasoconstriction, but at the same time, improved cerebral tissue oxygenation which protected the cells from damage.

The first article written by Holbach *et al.* studying the effect of HBO on glucose metabolism was published in 1972[58]. The main objective of this study was to determine the limits of O_2 tolerance in severely brain-injured patients to advance the use of HBO in the treatment of TBI. In this study, the effects of different HBO pressures (1–3 ATA) on cerebral glucose metabolism were studied in ten patients with severe TBI. The $AVDO_2$, arterial–venous differences of glucose (AVDG), lactate (AVDL) and pyruvate were taken. The glucose oxidation quotient (GOQ), which indicates cerebral glucose oxidative metabolism, was then calculated. At 1.5 ATA, a well-balanced cerebral glucose metabolism was maintained, indicated by a normal GOQ of 1.35. There was also a decrease in lactate and lactate/pyruvate ratio. However, Holbach *et al.* found that exposure of HBO at 2 ATA led to a decrease in oxidative glucose metabolism shown by a significantly reduced uptake of O_2 in comparison to glucose as well as a rise in lactate and lactate/pyruvate levels[58]. They found that the increased pressure interfered with oxidative energy formation and led to a compensatory increase of anaerobic energy production and hyperglycolysis.

By 1973, Holbach wrote: 'The real indication for the hyperbaric oxygen therapy is the deficiency of oxygen in the brain tissue because brain hypoxia is an essential factor of...secondary hypoxic brain lesions'[59]. He reviewed his past work, stating that HBO caused a marked rise in arterial O_2 pressure (8–10-fold increment at 1.5 ATA and 12-fold increment at 2 ATA), while the arterial O_2 pressure in the jugular bulb venous flow rose only slightly resulting in a marked increase in cerebral

$AVDO_2$. He also reiterated the findings of the 1972 study which showed that 1.5 ATA was the ideal pressure based on oxidative glucose metabolism. Finally, the results of a randomized trial between patients treated with 1.5 versus 2.0 ATA were described. Two hundred and sixty-seven HBO treatments were given to 102 patients: 50 patients treated with 1.5 ATA and 52 treated with 2.0 ATA. Forty-eight percent of the patients treated with 1.5 ATA had a good outcome versus 25% of the patients treated with 2.0 ATA. This improvement in functional outcome was statistically significant.

An important clinical study was published by Holbach *et al.* in 1974[14]. This paper strongly suggested that HBO applied systematically may improve the outcome of patients who were severely brain-injured. The study included 99 patients with traumatic midbrain syndrome, every other one of whom was treated with HBO at 1.5 ATA for 30 minutes. Each patient received between one and seven treatments which was determined on each patient's response to the HBO. The overall mortality rate for the 49 HBO-treated patients was 33% as compared to the control patients which was 74%. Functional outcome also was improved with 33% of the HBO-treated patients having a good outcome compared to 6% of the control patients. Patients with cerebral contusions less than 30 years of age were particularly benefited by HBO. They found that the increased survival and functional outcome in the HBO-treated group was secondary to decreased ICP as well as improved oxidative glucose metabolism.

The final publication by Holbach *et al.* was in 1977 (Ref. 60). This study measured the effect of HBO at 1.5 and 2 ATA on cerebral glucose metabolism in 23 TBI patients and seven anoxic brain-injured patients. Many of their previous findings on the effect of pressure on glucose metabolism were replicated in this study. They found that the injured brain would not tolerate HBO exposure at 2 ATA for 10–15 minutes, but exposure at 1.5 ATA for 35–40 minutes was well tolerated and glucose metabolism was improved. An important finding for future work was that the $AVDO_2$ values remained unchanged after the 1.5 ATA HBO treatments from baseline measurements.

Another clinical study was published by Artru *et al.*, evaluating the effectiveness of HBO in the treatment of severely brain-injured patients[15]. The study was a prospective trial of 60 patients randomized into an HBO treatment group and a control group. The HBO was administered at 2.5 ATA for 60 minutes. The treatment sequence was ten daily sessions, no session for 4 days, followed by ten more daily sessions until the patient either recovered consciousness or died. There was a time delay between injury and onset of HBO treatment averaging 4.5 days. Only 17 of the 31 patients received four daily treatments in the first week secondary to treatment interruptions. No difference in mortality at year 1 was seen between the two groups; however, infectious complications were the primary reason for death in both groups. Functional outcome was improved at month 1, in younger patients treated with HBO, who had a clinical picture of brainstem contusion. The authors found that the delay in treatment and frequent interruptions of treatment may have led to the study's poor results.

A second paper written by Artru *et al.*, also published in 1976, studied the effect of HBO on cerebral metabolism in severely brain-injured patients[61]. Six patients were treated with HBO at 2.5 ATA, timing between dives is not known. CBF, $AVDO_2$, AVDG and AVDL as well as CSF parameters were measured 2 hours pre-dive and 2 hours post-dive. The cerebral metabolic rates of oxygen ($CMRO_2$), glucose (CMRG) and lactate (CMRL) were calculated from those measurements. Pre-dive arterial and CSF lactate levels were found to be high while pre-dive CBF and $CMRO_2$ were lower than normal. They found that the $AVDO_2$ remained constant before and after the dives as had Holbach *et al.*[60]. The CBF was raised in patients who had low CBF values before the dive and was reduced in the patients who started with a high CBF. Each patient's $CMRO_2$ values followed the direction of their CBF. The effects of the HBO treatment did not last until the next pre-dive measurement and the patients reacted to each HBO treatment consistently. The spinal CSF lactate, CMRL and CMRG did not significantly change. The authors concluded that HBO can improve CBF when there is cerebral edema or intracranial hypertension.

In 1982 Sukoff *et al.* published an article studying the effect of HBO on CBF and ICP in TBI[12]. Their theory was that HBO reduced ICP by decreasing CBF but concomitantly increased cerebral oxygenation leading to a decrease in cerebral ischemia. Entered into the study within 6 hours of injury, 50 comatose TBI patients were treated with HBO at 2 ATA for 45 minutes every 8 hours for 2–4 days. The ICP was decreased in all patients in whom measurements were obtained. This reduction ranged between 4 and 21 mmHg below the pre-dive level and was sustained for 2–4 hours after HBO treatment was completed. Sukoff *et al.* recorded only the lowest ICP value during the HBO treatment and did not report all ICP measurements recorded throughout the dive[12]. There were no reports of pulmonary toxicity. They found that additional studies on the effect of HBO on ICP and cerebral metabolism were needed.

The above investigations of HBO had several weaknesses. Most of the protocols were not uniform and the number of subjects was small. Although Holbach *et al.* had shown that the ideal depth was 1.5 ATA for treatment of TBI, HBO was delivered at 2–3 ATA in most of the experimental and clinical studies[14,58–60]. In the clinical trials, the severity of brain injury is not known as Glasgow coma scale (GCS) scoring was not used. In addition, none of the trials were truly randomized. Despite these shortcomings, positive results on the efficacy of HBO in TBI were consistently found.

The first paper to show that HBO had a persistent effect on cerebral glucose metabolism following treatment was published by Contreras *et al.*[62]. The authors measured glucose utilization with the autoradiographic 2-deoxyglucose technique in rats injured by a focal

parietal cortical freeze lesion. This cold lesion was felt to correspond with a focal brain contusion. Four groups of rats were used: (1) sham-lesioned group, no treatment; (2) sham-lesioned, HBO treatment; (3) cold-lesioned, no treatment; (4) cold-lesioned, HBO treatment. The HBO treatments at 2 ATA for 90 minutes were carried out daily for 4 consecutive days. Initially, glucose utilization was decreased throughout the brain, especially ipsilateral to the lesion. Glucose utilization, however, tended to be increased 5 days after injury in the HBO-treated cold-lesioned rats as compared to the control cold-lesioned group. This improvement reached statistical significance in five of the 21 structures examined, which were the auditory cortex, the medial geniculate body, the superior olivary nucleus, the lateral geniculate body ipsilateral to the lesion and the mamillary body. An interesting finding was that HBO decreased glucose utilization in sham-lesioned rats. Their results indicate that HBO improves glucose utilization in a cold-lesion rat model, especially in the gray matter structures close to the actual lesion. Their novel finding was that the increase persisted for at least 1 day after termination of HBO exposure. They were unsure of the mechanism involved with this persistence, but felt that further studies were indicated.

A paper which studied the effects of HBO on the blood–brain barrier was published by Mink *et al.*[63]. Rabbits were subjected to cerebral ischemia by CSF compression. They were allowed to reperfuse for 30 minutes and then either treated with HBO at 2.8 ATA for 125 minutes followed by 90 minutes of 100% FiO_2 or with 100% O_2 for 215 minutes. CBF and vascular permeability were measured at the end of the reperfusion period and 90 minutes after termination of the treatments. HBO treatment statistically lowered CBF in the HBO-treated group as compared with the controls. Vascular permeability also was statistically lowered by 16% in the gray matter and 20% in the white matter. Somatosensory evoked potentials (SEP) were similar between both groups. The authors concluded that HBO was promoting the blood–brain barrier integrity following global cerebral ischemia in a rabbit model. CBF also was reduced and this effect was not associated with a reduction in the SEP recovery. The results suggested that if there were any detrimental effects of free radical generation with HBO treatment, they were outweighed by the beneficial effects of HBO.

An important paper investigating the mechanisms by which HBO improved ischemic tissue O_2 capacitance was published by Siddiqui *et al.*[64]. The authors measured subcutaneous tissue O_2 treatment in an ischemic rabbit ear model before, during and after HBO treatment followed by 100% O_2 versus those treated only with 100% O_2. The HBO treatment, which was at 2 ATA for 90 minutes, was performed daily for 14 treatments. The tissue responsiveness, measured by O_2 tissue tension, was found to increase on successive days from an ischemic baseline to well above a non-ischemic level. The authors found that there was 'a consistent and striking response to 100% oxygen (at 1 ATA) by ischemic tissue undergoing serial hyperbaric oxygen therapy'. This responsiveness was not found in tissue that was treated only with 100% O_2 at 1 ATA. The group asserted that this tissue responsiveness indicates the tissue's ability to accept and potentially use O_2 and that HBO was responsible for this change. They found that cells in the ischemic region may see the supraphysiologic elevation of tissue O_2 partial pressure as a trigger that signals that enough O_2 is in the environment to proceed with normal healing. Subsequent exposure to 100% O_2 reinforces this signal and also supplies the O_2 needed to continue the repair. They concluded that 'molecular oxygen, when delivered at high pressure, can function both as a respiratory metabolite and as a signal transducer'.

Rockswold *et al.* published the first modern prospective randomized clinical trial on the efficacy of HBO in the treatment of severely brain-injured patients[6]. All patients who were entered had suffered closed head injury with a GCS score of 9 or less. The patients were entered into the study between 6 and 24 hours post-injury. One hundred and sixty-eight severely brain-injured patients were randomized into two groups: the first group receiving HBO treatments and the second serving as a control group. Eighty-four patients received HBO with 100% O_2 at 1.5 ATA for 60 minutes. Treatments were given every 8 hours for 14 days unless the patient began following commands or became brain dead. Treatments were discontinued if the patient required a fraction of inspired oxygen (FiO_2) of 50% or greater to maintain an arterial PO_2 greater than 70 mmHg. The GOS was used as the primary tool for assessing outcome. Of the 168 patients, only two control patients were lost to follow-up at month 12.

The mortality rate for the 84 HBO-treated patients was 17% and for the 82 control patients was 32% ($p<0.05$). This improvement suggests a 50% relative reduction in mortality. In addition, mortality rate was improved in specific subgroups. In the 47 patients with ICP values persistently greater than 20 mmHg, the mortality rate was 21% as opposed to 48% mortality in the 40 patients with elevated ICP who served as controls ($p<0.02$). Functional recovery was evaluated 12 months post-injury using the GOS. Favorable outcome was defined as good recovery or moderate disability. Overall, there was no significant improvement in favorable outcome in the 84 patients treated with HBO in comparison to the 82 control patients. However, some specific subgroups did show improved favorable outcome. The 33 patients with surgically evacuated mass lesions had a 45% favorable outcome at year 1 as opposed to a 34% favorable outcome in the 41 patients with surgically evacuated mass lesions who served as control. This indicates a 33% relative improvement. It is now thought that with an appropriately increased 'n', this difference would be statistically significant. Mean peak ICP was significantly reduced in HBO-treated patients as opposed to controls.

Of major importance is the fact that the 84 patients in the treatment group received a total of 1688 HBO treatments for an average of 21 treatments. Considering the number of treatments delivered, relatively few

complications occurred. They were all pulmonary in nature, manifested by an increased FiO_2 requirement and frequently, chest X-ray infiltrates. In ten patients, the HBO treatments were stopped. All pulmonary changes were reversible. There were no permanent sequelae that occurred from the 1688 HBO treatments that were delivered.

This clinical outcome study showed that HBO can be administered to severely brain-injured patients safely and systematically and that mortality rates for severely brain-injured patients are reduced by ~50% with HBO treatments, particularly in patients with GCS scores of 4–6, those with mass lesions and those with increased ICP. These three factors are interrelated and without HBO treatment, the mortality rate would be the highest in these groups of patients because all are indicative of poor prognosis. Thus, through reducing ICP and probably improving aerobic glucose metabolism, HBO allowed these severely brain-injured patients to survive. The authors were unsure why the functional recovery overall was not improved with this treatment paradigm but hypothesized that too much O_2 was given to patients with less severe injuries, i.e. higher GCS score, contusion or normal ICP. They found that the protocol should be more individualized.

Many questions persisted about the efficacy and application of HBO in TBI following the above prospective randomized clinical study. Further investigation was needed to elucidate the potential metabolic effects of HBO on severely brain-injured patients. A prospective, clinical physiologic study, therefore, was undertaken to determine the effects of HBO on CBF, cerebral metabolism and ICP[7].

Thirty-seven patients treated for severe TBI were entered into the study within 24 hours of admission. All patients had a GCS score 8 or less and CT scan scores were ≥II in conformance with the classification system of the Traumatic Coma Data Bank. The patients received HBO with 100% O_2 at 1.5 ATA for 60 minutes. The mean time from injury to initial HBO treatment was 23 hours. Treatment was administered on subsequent days for a total of five treatments. CBF using the nitrous oxide method, $AVDO_2$, $CMRO_2$, ventricular CSF lactate levels and ICP values were obtained 1 hour before HBO and 1 and 6 hours post-HBO. The patients were then assigned to reduced, normal or raised categories according to the CBF classification system developed by Obrist *et al.* and modified by Robertson *et al.*[65,66].

In patients in whom CBF levels were reduced before HBO, both CBF and $CMRO_2$ were raised 1 and 6 hours after HBO (p=0.001). In patients in whom CBF levels were normal before HBO, both CBF and $CMRO_2$ levels were increased at hour 1 (p<0.05), but not at hour 6. CBF was reduced 1 and 6 hours after HBO (p=0.007), but $CMRO_2$ was unchanged in patients who exhibited raised CBF before HBO.

Levels of CSF lactate were consistently decreased 1 and 6 hours after HBO, regardless of the patients' CBF category before undergoing HBO (p=0.011). Pre-dive CSF lactate levels for individual HBO treatments were inversely related to the pre-dive CBF values demonstrating that in those HBO sessions in which patients began with a reduced CBF value, CSF lactate pre-treatment levels were significantly greater than those seen in HBO in which patients began with normal or raised CBF (p=0.003). This finding may indicate that patients with reduced pre-dive CBF were the most ischemic or had the most severe cellular dysfunction in the brain and responded to HBO treatment most dramatically.

ICP was measured before, during the HBO treatment and until the next HBO treatment. The ICP values rose throughout the dive except for a trend for patients with elevated ICP (≥15 mmHg) to improve during the pressurization phase and the first 15 minutes of the HBO treatment. Patients with elevated ICP also showed a consistent and highly significant decrease in their ICP from the time of the completion of the HBO treatment to 6 hours post-treatment (p=0.006).

The results of this study indicate that HBO may have improved the ability of ischemic or damaged brain tissue to use the O_2 received in baseline FiO_2 for at least 6 hours following the HBO. This led to improved $CMRO_2$ and decreased CSF lactate levels, which also persisted for at least 6 hours, indicating a shift toward aerobic metabolism. The authors hypothesized that CBF rises in response to this increased cerebral metabolism. When CBF and $CMRO_2$ are normally metabolically coupled, the ratio between them does not change; in other words, the $AVDO_2$ remains constant. This trend for HBO to normalize metabolic coupling of CBF and cerebral metabolism was the most apparent in patients with reduced CBF or with ischemia as documented by high lactate levels.

The authors found that the potentially noxious stimuli of heat and pressure in the paranasal sinuses may have overridden any benefit that HBO had on the patient's ICP during treatment. However, in patients who began their dive with a high ICP, HBO reduced their ICP (≥15 mmHg) for at least 6 hours following treatment. In this study, HBO also lowered CBF in patients who began their treatment with a raised CBF and did so without significantly reducing their $CMRO_2$. Raised CBF or hyperemia has been shown to be related to increased ICP, brain edema and poor outcome. The authors felt that HBO may promote blood–brain barrier integrity, reducing cerebral edema and hyperemia, which in turn helped to lower elevated ICP.

In 2004, an important basic science article was published by Daugherty *et al.* studying the mechanism of action that HBO has on TBI[9]. The authors produced strong supporting experimental data for clinical observations of Rockswold *et al.*[7]. Four groups of rats were compared: (1) sham-injured, 30% FiO_2 for 4 hours; (2) sham-injured, 1 hour HBO (1.5 ATA) followed by 3 hours of 100% FiO_2 at 1 ATA; (3) fluid percussion injured, 30% FiO_2 for 4 hours; (4) fluid percussion injured, 1 hour HBO (1.5 ATA) followed by 3 hour 100% FiO_2 at 1 ATA. Fluid percussion injury was delivered at 2.1 ± 0.05 ATA to the rats[67,68]. PtO_2 levels were measured by a Licox probe into the cortex near the cortical hippocampal junction. This placement allowed

for the measurement of brain PtO_2 under the injury site. *Ex vivo* measurements of global brain tissue oxygen consumption (VO_2). were made using the Cartesian diver microrespirometer methodology described by Levasseur *et al.*[69]. *Ex vivo* measurements of mitochondrial metabolic activity (redox potential) were carried out in a synaptosomal preparation to enrich for mitochondria. Mitochondrial redox potential was measured using an Alamar blue fluorescence technique[70,71].

Brain PtO_2 was significantly improved in both the injured and sham-injured animals that received HBO treatment as compared to the ones receiving only 30% O_2. Injured animals tended to have a lower brain PtO_2 levels as baseline compared to the sham-injured ones. Baseline brain PtO_2 levels were 37.7 mmHg in injured animals receiving 30% O_2. This value went to ~103 mmHg on 100% O_2 at 1.0 ATA and finally to 247 mmHg on HBO at 1.5 ATA. The dramatic relative 250% increase in brain PtO_2 levels, when going from 100% O_2 at 1 ATA to 100% O_2 at 1.5 ATA, was not clear. Under normobaric conditions, the amount of dissolved O_2 in the blood is relatively small (0.3 ml/dl in air at atmospheric pressure). HBO at 1.5 ATA increases the amount of dissolved O_2 by ten-fold (3.2 ml/dl), therefore increasing the arterial PO_2. One hypothesis for explaining the relatively high brain PtO_2 in relationship to arterial PO_2 is that this dissolved O_2 in plasma is more readily available to brain tissue than hemoglobin-bound O_2.

The combined HBO/100% FiO_2 treatment paradigm described also caused a highly significant increase in global VO_2 in both injured and sham-injured animals when compared to control animals receiving 30% O_2. Brain tissue VO_2 is a marker for cerebral aerobic metabolism and corresponds to $CMRO_2$ values used clinically in patients. CBF and VO_2 are closely coupled and respond to cellular activity. Daugherty *et al.* felt that the findings of increased VO_2 after HBO treatment strongly support that HBO improves aerobic metabolism in the injured brain[9].

Mitochondrial redox potential was significantly reduced by the fluid percussion injury when compared to sham-injured animals in both the HBO and 30% FiO_2 groups at the completion of 1 hour of treatment. However, following the 1 hour HBO treatment plus 3 hours of 100% O_2 at 1 ATA, mitochondrial redox potential was reversed to near sham-injured animal levels. When the authors compared the effects of the different treatments at hour 4, the injured animals that had received the HBO treatment had significantly increased mitochondrial redox potential in all areas of the brain sampled when compared to the injured animals that had received 30% O_2. These data indicate that mitochondrial function may be depressed after TBI, but there is a potential for mitochondrial functional recovery and that HBO can enhance this recovery.

Recent experimental evidence in the same lateral fluid percussion TBI rat model has demonstrated improved cognitive recovery, increased cerebral ATP levels and reduced hippocampal neuronal cell loss with HBO followed by normobaric hyperoxia[10]. For the cognitive recovery portion of the study, 205 rats were divided into four groups 15 minutes after injury: (1) sham-injured; (2) fluid percussion injured, 30% FiO_2; (3) fluid percussion injured, 100% O_2 in the HBO chamber at 1.5 ATA for 1 hour and at 1 ATA for additional 3 hours; (4) fluid percussion injured, 100% O_2 in the HBO chamber at 1 ATA for 4 hours. On days 11–15 following injury, cognitive function was assessed by the Morris Water Maze test. The results demonstrated that when compared to sham animals, all three injured groups described above had longer goal latencies. However, the combined HBO/FiO_2-treated group showed significantly shorter goal latency than the other two groups for all time points. By day 15, the cognitive deficit was markedly attenuated in the HBO/100% O_2-treated group, but not in the 100% O_2-treated group or control animals.

For ATP measurement, the rats in each group were given only 1 hour of treatment, whether it was 30% O_2, HBO or normobaric hyperoxia. The combination of HBO and 100% O_2 was not studied. ATP was extracted from the cerebral cortex and measured using high performance liquid chromatography system. Immediately following injury, ATP levels were significantly decreased in all injured animals when compared to sham-injured animals. However, after 1 hour of treatment, both groups of animals that received hyperoxia had significantly elevated ATP levels when compared with the injured animals that received 30% O_2. In fact, the ATP levels were close to the levels of the sham-injured group.

Twenty-one days post-injury, four rats in each group were killed to assess hippocampal neuronal loss. Cranial sections throughout the hippocampus were examined with an Olympus Image System Cast Program. The HBO/100% FiO_2 combined group had significantly reduced injury-induced cell loss in the CA2–3 region of the hippocampus when compared to control or animals receiving normobaric hyperoxia alone. No significant differences in peroxide, peroxynitrite or free radical production between the sham-injured animals and the injured animals treated with 30% O_2, 100% O_2 or HBO 1 or 4 hours post-treatment were found. The results of this study strongly corroborate the findings that HBO used in combination with normobaric hyperoxia enhances cellular metabolism and supports the concept that this enhancement provides a protective effect for severe TBI.

POTENTIAL MECHANISM OF HBO

Historically, the mechanism through which HBO worked was found to be vasoconstriction of the cerebral blood vessels which led to decreased CBF and ICP. The vasoconstriction was not found to be deleterious because O_2 availability to the injured cells was greatly increased[11,13]. As experimental research continued and more evidence accumulated, however, HBO appeared to be decreasing cerebral edema and stabilizing the blood–brain barrier as well[52,55,63]. Recent clinical studies on the effect of HBO corroborate these findings

with elevated ICP being improved persistently after treatment[6,7,12].

HBO appears to improve aerobic metabolism in severely brain-injured patients. Following severe TBI, there is a relative energy crisis with depression of cerebral mitochondrial function. Impaired mitochondrial respiration results in a shift from aerobic to anaerobic metabolism with resultant increased lactate and reduced ATP production[29,30]. At the same time, delivery of O_2 to the brain tissue is reduced by both decreased local CBF as well as diminished O_2 diffusion secondary to cerebral edema. HBO allows the delivery of supranormal amounts of O_2 to the injured brain cells through increasing dissolved O_2 in the blood and improved CBF[7,9]. In addition, work by several investigators suggests that HBO allows the injured brain to use baseline amounts of O_2 more efficiently following treatments and has a persistent effect on the injured brain tissue[7,9,60–62]. There is a growing amount of experimental animal evidence that this change occurs at the mitochondrial level[9,10]. The exact mechanism by which HBO may enhance mitochondrial recovery is unknown.

SAFETY AND OXYGEN TOXICITY ISSUES

Most neurosurgeons treating severe TBI are only familiar with HBO treatment in a relatively vague way. Even among neurosurgeons more familiar with the technique, the idea of placing an intubated, severely brain-injured patient with multiple injuries into an HBO chamber, particularly a monoplace, seems prohibitive[72]. One of the challenges in establishing HBO as an accepted therapy for severe TBI is to establish its safety as well as the efficacy of the treatment.

Fortunately, for both the TBI patient and the treating physician, the landmark investigations of Holbach *et al.* established the ideal HBO treatment pressure at 1.5 ATA[58–60]. This is a relatively 'shallow dive' as far as HBO treatment protocols are concerned, which are typically in the 2.0–3.0 ATA level. The intermittent 60 minute HBO treatment administered every 6–8 hours at 1.5 ATA greatly reduces potential safety and toxicity issues.

Based on our own past and continuing investigations, as well as that of Weaver *et al.* placing severe TBI patients in either a monoplace or multiplace HBO chamber at 1.5 ATA for 60 minutes is a very low risk procedure[6,7,73–76]. Monoplace chambers are much less expensive than multiplace chambers and can be placed in or near the intensive care unit. In fact, the monoplace chamber becomes an extension of the critical care environment. Continuous monitoring of ICP, mean arterial pressure (MAP), cerebral perfusion pressure (CPP), end tidal CO_2 and brain tissue oxygen can be performed. In addition, central venous pressure or Swan-Ganz catheter monitoring are carried out if needed. Careful evaluation of the patient's pulmonary status before HBO treatment is critical. In our work, we have regarded a baseline FiO_2 requirement of greater than 50% and a positive end expiration pressure of greater than 10 to maintain adequate oxygenation as contraindications to HBO. It is essential to maintain adequate ventilation throughout the treatment. In the case of an emergency, an intubated ventilated patient can be decompressed and out of the chamber in 2 minutes. We routinely perform myringotomy to reduce patient stimulation during treatment and thereby, ICP[6].

The lung is the organ most commonly damaged by hyperoxia because the O_2 tension in the lungs is substantially higher than in other tissues[77]. The mechanism by which pulmonary injury occurs has been termed 'oxidative stress'[78,79]. Central to this process is the release of proinflammatory cytokines by alveolar macrophages, specifically IL-8 and IL-6, and the subsequent influx of activated cells into the alveolar air space[80,81]. Measurement of these proinflammatory cytokines in bronchial alveolar lavage has been shown to be predictive of acute lung injury and pulmonary infection in exposure to super physiologic concentrations of inspired O_2[82].

The concept of 'unit pulmonary toxic dose' (UPTD) has been developed and allows comparison of the pulmonary effects of various treatment schedules of hyperoxia[83,84]. One UPTD is equal to 1 minute of 100% O_2 at 1 ATA. Appropriate conversion factors (Kp), that is, multipliers of 1 minute of 100% O_2 at 1 ATA, allow one to quantitate the pressure (ATA) of the O_2 exposure. In general, it is recommended that total O_2 exposure in a single treatment be limited to a UPTD of 615 or less. The extreme limit of a single O_2 exposure is 1425 UPTD. This dose will produce a predicted 10% decrease in vital capacity in a normal individual. A 1 hour HBO treatment at 1.5 ATA is equal to 60 × 1.78 Kp or 106.8 UPTD. In our first study, 1 hour treatments at 1.5 ATA were delivered every 8 hours producing 320 UPTD per day[6]. The 24 hours of 100% O_2 at 1 ATA, which was described in the recent article by Tolias *et al.*, is the equivalent of 1440 UPTD[8]. This number exceeds the extreme upper limit for a single O_2 exposure. Therefore, relatively speaking, a 1 hour HBO treatment of 1.5 ATA delivers a low dose of O_2. In the clinical trial described previously in which 84 TBI patients received 1688 HBO treatments, no permanent sequelae resulted[6]. Pulmonary complications occasionally occurred (ten of 84 patients), but all were reversible.

Oxygen, especially under increased pressure, also may cause potential cerebral toxicity. Brain tissue is especially vulnerable to lipid peroxidation because of its high rate of O_2 consumption and high content of phospholipids. Additionally, the brain has limited natural protection against free radicals, i.e. it has limited scavenging ability, poor catalase activity and is rich in iron, which is an initiator of radical generation in brain injury[25,85–87]. There are experimental studies demonstrating increased formation of reactive O_2 radicals and secondary lipid peroxidation in the brain, but the depth and duration of HBO treatment in theses studies are much greater than used in our clinical investigations[88–90]. There is no clinical evidence for cerebral toxicity using an HBO treatment paradigm of 1.5 ATA

for 60 minutes. However, to further evaluate this issue, we are monitoring ventricular CSF F2-isoprostane which is isometric to cyclo-oxygenase and is derived from prostaglandin F2[91,92]. CSF F2-isoprostane is exclusively produced from free radical catalyzed peroxidation of arachidonic acid. It is a specific quantitative biomarker of lipid peroxidation *in vivo* in the brain. F2-isoprostane values have not been elevated in our current study (unpublished data).

In conclusion, HBO treatments at a depth of 1.5 ATA can be delivered to the severe TBI patient with or without multiple injuries in either a monoplace or multiplace chamber with relative safety and low risk of O_2 toxicity.

PRESENT AND FUTURE DIRECTIONS

The authors are currently carrying out a prospective, randomized clinical trial for severe TBI patients designed as three-treatment comparison, i.e. HBO, normobaric hyperoxia and control, funded by the National Institute of Neurological Disease and Stroke. HBO is delivered for 60 minutes at 1.5 ATA and normobaric hyperoxia (100% FiO_2) for 3 hours. The treatments are given every 24 hours for 3 days. Recent studies have described normobaric hyperoxia (100% FiO_2) as a method of delivering supernormal levels of O_2 to severe TBI patients[8,27]. Improvement in cerebral metabolism and reduced ICP have been described. The relative ease of administration and its inexpense require that normobaric hyperoxia be evaluated as an alternative treatment to HBO.

This is not a clinical outcome study. However, surrogate outcome variables which predict and correlate with clinical outcome will be studied. They are measured before initiation of therapy, during administration of therapy, and for 24 hours following therapy. Continuously monitored outcome variables include ICP, PtO_2, microdialysate lactate, glucose, pyruvate and glycerol. CBF, $AVDO_2$, $CMRO_2$, CSF lactate, F2-isoprostanes and bronchial lavage fluid (IL-8 and IL-6 assays) are being obtained once before treatment, during treatment, and 1 and 6 hours post-treatment. The results of the trial will allow a direct comparison of HBO and normobaric hyperoxia in terms of their treatment efficacy on the surrogate outcome variables as well as their relative toxicity. In addition, post-treatment effects will be compared statistically to pre-treatment values. The duration of the effect will be determined. Traumatic brain injury is very heterogeneous in terms of lesions and severity. The study will allow us to determine which severe TBI patients respond to therapy in terms of their GCS scores and lesion types.

The work described above by Daugherty and Zhou from the laboratory at the Medical College of Virginia, has prompted a fourth treatment arm in this study[9,10]. That is a combination of HBO for 60 minutes at 1.5 ATA followed by 3 hours of 100% FiO_2 at 1.0 ATA. The hypothesis to be tested is that improvement in cerebral metabolism does not occur during the HBO treatment, but HBO treatment results in improved use of O_2 by restoring mitochondrial function in the hours following treatment.

Following completion and analysis of the above clinical trial, our goal is to use positron emission tomography (PET) scanning in testing the hypothesis that the optimum HBO treatment paradigm improves mitochondrial dysfunction and the energy depletion crisis which occurs following severe TBI in humans. Hovda and colleagues at University of California, Los Angeles (UCLA) have demonstrated a strong correlation between cerebral metabolism and neurological outcome in TBI[93–95]. Clinical improvement coupled to enhanced cerebral metabolism documented by PET scanning would provide strong evidence for the beneficial effect of HBO.

It remains to be seen whether the data accumulated will be compelling enough to institute HBO either alone or in combination with 100% FiO_2 as a standard treatment for severe TBI or whether a multicenter clinical outcome trial will be required. The authors are reasonably confident based on this review and their experience that in either case, HBO will become a significant treatment for patients suffering a severe TBI.

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