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A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury

Clinical article

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Object. Oxygen delivered in supraphysiological amounts is currently under investigation as a therapy for severe traumatic brain injury (TBI). Hyperoxia can be delivered to the brain under normobaric as well as hyperbaric conditions. In this study the authors directly compare hyperbaric oxygen (HBO_2) and normobaric hyperoxia (NBH) treatment effects.

Methods. Sixty-nine patients who had sustained severe TBIs (mean Glasgow Coma Scale Score 5.8) were prospectively randomized to 1 of 3 groups within 24 hours of injury: 1) HBO_2, 60 minutes of HBO_2 at 1.5 ATA; 2) NBH, 3 hours of 100% fraction of inspired oxygen at 1 ATA; and 3) control, standard care. Treatments occurred once every 24 hours for 3 consecutive days. Brain tissue PO_2, microdialysis, and intracranial pressure were continuously monitored. Cerebral blood flow (CBF), arteriovenous differences in oxygen, cerebral metabolic rate of oxygen ($CMRO_2$), CSF lactate and F2-isoprostane concentrations, and bronchial alveolar lavage (BAL) fluid interleukin (IL)–8 and IL-6 assays were obtained pretreatment and 1 and 6 hours posttreatment. Mixed-effects linear modeling was used to statistically test differences among the treatment arms as well as changes from pretreatment to posttreatment.

Results. In comparison with values in the control group, the brain tissue PO_2 levels were significantly increased during treatment in both the HBO_2 (mean ± SEM, 223 ± 29 mm Hg) and NBH (86 ± 12 mm Hg) groups ($p < 0.0001$) and following HBO_2 until the next treatment session ($p = 0.003$). Hyperbaric O_2 significantly increased CBF and $CMRO_2$ for 6 hours ($p \leq 0.01$). Cerebrospinal fluid lactate concentrations decreased posttreatment in both the HBO_2 and NBH groups ($p < 0.05$). The dialysate lactate levels in patients who had received HBO_2 decreased for 5 hours posttreatment ($p = 0.017$). Microdialysis lactate/pyruvate (L/P) ratios were significantly decreased posttreatment in both HBO_2 and NBH groups ($p < 0.05$). Cerebral blood flow, $CMRO_2$, microdialysate lactate, and the L/P ratio had significantly greater improvement when a brain tissue $PO_2 \geq 200$ mm Hg was achieved during treatment ($p < 0.01$). Intracranial pressure was significantly lower after HBO_2 until the next treatment session ($p < 0.001$) in comparison with levels in the control group. The treatment effect persisted over all 3 days. No increase was seen in the CSF F2-isoprostane levels, microdialysate glycerol, and BAL inflammatory markers, which were used to monitor potential O_2 toxicity.

Conclusions. Hyperbaric O_2 has a more robust posttreatment effect than NBH on oxidative cerebral metabolism related to its ability to produce a brain tissue $PO_2 \geq 200$ mm Hg. However, it appears that O_2 treatment for severe TBI is not an all or nothing phenomenon but represents a graduated effect. No signs of pulmonary or cerebral O_2 toxicity were present. *(DOI: 10.3171/2009.7.JNS09363)*

Key Words • **hyperbaric oxygen** • **normobaric hyperoxia** • **oxygen toxicity** • **traumatic brain injury** • **cerebral metabolism** • **intracranial pressure**

Abbreviations used in this paper: $AVDO_2$ = arteriovenous differences in oxygen; BAL = bronchial alveolar lavage; CBF = cerebral blood flow; $CMRO_2$ = cerebral metabolic rate of oxygen; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; HBO_2 = hyperbaric oxygen; ICP = intracranial pressure; ICU = intensive care unit; IL = interleukin; L/P = lactate/pyruvate; NBH = normobaric hyperoxia; OEF = oxygen extraction fraction; PEEP = positive end expiration pressure; P/F = PaO_2/FiO_2; PvO_2 = partial pressure of venous oxygen; ROS = reactive oxygen species; TBI = traumatic brain injury; TIL = therapeutic intensity level; UPTD = unit pulmonary toxicity dose.

Traumatic brain injury continues to be a major cause of death and disability in both civilian and military populations throughout the world. One and one-half million people suffer a TBI each year in the US alone, and ~ 1 million of them require an emergency room visit; 500,000 are hospitalized and 50,000 die.[13,47] These results mean direct and indirect costs of at least $56 billion annually for the US. Despite the tremendous negative impact on societies throughout the world and many multicenter therapeutic trials, no specific treatment for TBI is available.[47,66]

Although severe TBI results in marked heterogeneous structural pathology, there are common metabolic pathways leading to cellular energy failure.[83,87,94,109] There is evidence of ischemia in the first 24 hours after injury, resulting in decreased O_2 delivery that is inadequate to maintain efficient oxidative cerebral metabolism.[8,9,102] This metabolic state appears to trigger a marked increase in the glycolytic metabolism of glucose.[6,7,37] This relatively inefficient anaerobic metabolism results in the depletion of cellular energy. A cascade of biochemical events leads to mitochondrial dysfunction and a prolonged period of hypometabolism.[7,46,87,88,99] Diffusion barriers to the cellular delivery of O_2 develop and persist.[53] The degree to which cerebral oxidative metabolism is restored correlates with clinical outcome.[31] In addition, traumatic insult to the brain results in hematomas, contusion, and cerebral edema, all of which lead to intracranial hypertension. Intracranial hypertension is the major treatable cause of deterioration and death from severe TBI.[41]

In recent years there has been promising animal and clinical research in the area of hyperoxia as therapy, including HBO_2, for severe TBI.[18,69,72,79,80,94,95,110] The use of HBO_2 in TBI treatment has been controversial. The availability and expense of HBO_2 chambers, O_2 toxicity, and safety concerns have been at the forefront of this controversy. In truth, complications from HBO_2 have been rare and reversible in our experience. Historically, HBO_2 has been seen as a mechanism to decrease CBF and ICP while increasing O_2 availability to injured brain cells.[59,91,92] As more sophisticated techniques have become available in both experimental and clinical TBI studies, however, HBO_2 appears to restore mitochondrial function by greatly increasing the O_2 delivery diffusion gradient, which subsequently improves cerebral aerobic metabolism after brain injury.[18,80,95,109,110] Clinically, HBO_2 has been shown to decrease mortality rates and improve functional outcome in severely brain-injured patients.[1,36,79]

Another method of supernormal O_2 delivery is increasing the FiO_2 to 100% at normobaric pressure. Normobaric hyperoxia therapy is a potentially attractive alternative to HBO_2 because of its ease of administration. Several studies have shown that as FiO_2 increases, there is a corresponding rise in brain tissue PO_2.[54,95,98] In addition, microdialysate lactate decreases, which likely indicates improvement in tissue hypoxia.[48,54,95] Note, however, that improvement in the microdialysate L/P ratio (an indicator of mitochondrial function) during treatment has been demonstrated in only 1 study, and the effect was of short duration.[94] In a direct comparison between HBO_2 and NBH in animal models of TBI, HBO_2 has clearly had a significantly more robust effect.[72,110] Zhou et al.[110] have shown that HBO_2 reduces the ischemic loss of neurons in the hippocampus and improves neurobehavioral outcome, which was not produced by NBH.

Our goal in the present study was to evaluate cerebral metabolism, ICP, and potential O_2 toxicity during a prospective, randomized clinical trial comparing hyperbaric and normobaric O_2 in patients with severe TBI. This study was not a clinical outcome trial, as dosing was not made at therapeutic intervals; rather, our purpose was to study the effect of hyperoxia and its duration on surrogate outcome variables that predict and closely correlate with clinical outcome.

Methods

The Human Subjects Research Committee at our institution approved the study protocol. Seventy-four patients treated for severe TBI at Hennepin County Medical Center, a Level I trauma center, were entered into a prospective, randomized clinical trial to evaluate the mechanisms of action of hyperoxia on cerebral metabolism and ICP. Five patients were withdrawn from the study because they met the exclusion criteria before treatment (Table 1); these exclusions included brain death (1 patient), midbrain hemorrhage with fixed midpoint pupils (1 patient), narcotic overdose with anoxic injury (1 patient), and an ability to follow commands (2 patients). The remaining 69 patients fit the proposed inclusion criteria, with an average age of 35 years and an average entry GCS score of 5.8 (Table 2). The male/female ratio was ~ 6:1. Fifty-eight percent of the patients had sustained multiple traumas. Intracranial hypertension, defined as an episode in which ICP was > 20 mm Hg for > 20 minutes during the 4-day study period, was present in 48% of the patients.

All patients had sustained a severe TBI, which was defined as a GCS score ≤ 8 after resuscitation. This score was determined when no effects from paralytic agents, sedation, alcohol, and/or street drugs were present. Patients were entered into the study within 24 hours of injury. Twelve patients were entered into the study after being admitted to the hospital with a mild or moderate TBI and whose status deteriorated to a GCS score ≤ 8 within 48 hours of injury. Computerized tomography scan scores were ≥ II, in conformance with the classification system of the Traumatic Coma Data Bank.[50] After study eligibility and a GCS score were established, informed consent was obtained from each participant. Randomization occurred immediately after consenting to participate in the study. All patients received intensive neurosurgical care closely paralleling that of the Brain Trauma Foundation's "Guidelines for the Management of Severe TBI, 3rd Edition."[11] This protocol included stabilization with early intubation while the patient was in the emergency department, surgical evacuation of significant hematomas, continuous monitoring of ICP, and treatment of ICP > 15 mm Hg. In accordance with our protocol, all patients received prophylactic phenytoin sodium.

Treatment Randomization

This randomized clinical trial was designed as a 3-treatment comparison: HBO_2, NBH, and standard care. The HBO_2 treatment consisted of 100% FiO_2 delivered for 60 minutes at 1.5 ATA. The NBH treatment consisted of 100% FiO_2 given for 3 hours at 1.0 ATA. Standard care was the control treatment.

Twenty-six patients were randomized to the HBO_2 group, 21 to the NBH group, and 22 to the control group. Originally, 20 patients were to be enrolled in each group. Early in the study, however, there were technical difficulties in obtaining accurate jugular venous blood gases. The research personnel drew the samples too quickly,

TABLE 1: Study inclusion and exclusion criteria*

Criteria	Description
inclusion	all closed-head trauma victims w/ GCS scores of 3–8 after resuscitation, w/o effects from paralytics, sedation, alcohol, &/or street drugs
	HBO_2 treatment to begin w/in 24 hrs after injury
	admission to hospital w/ a mild or moderate brain injury & deterioration w/in 48 hrs
	after injury to a GCS of 4–8, CT scan score of ≥2 in accordance w/ classification system of Traumatic Coma Databank
exclusion	GCS score >8
	bilat fixed mid-position pupils
	severe pulmonary injury requiring an FiO_2 >50% &/or PEEP >10 cm H_2O to maintain adequate oxygenation
	history of severe pulmonary disease (e.g., asthma or chronic obstructive pulmonary disease)
	unstable fractures (e.g., spine, pelvis, femur) preventing placement into HBO_2 chamber
	fixed coagulopathy
	pregnancy
	severe mental retardation or prior severe brain injury or stroke
	high-velocity penetrating injury to head
	multiple organ failure

* e.g. = for example.

which resulted in contamination of the venous blood gas samples with extracranial blood, namely, from the facial vein.[17,52] The saturation of jugular venous blood gas (SjO_2) measurements for these samples were spuriously high, with an average value of 89%. Unfortunately, a higher percentage of patients in the HBO_2 group (50%), compared with those in the control (25%) and NBH (15%) groups, was affected. Our statistician recommended that 6 more patients in the HBO_2 arm, 2 more in the control arm, and 1 more in the NBH arm be included to compensate for the affected patients but to maintain the randomization process. The patients were considered in all statistical analyses except for global cerebral metabolism (that is, $AVDO_2$, CBF, and $CMRO_2$). In addition, for each variable measured, some patients had missing data and so were not included in that particular statistical analysis. Differences in the number of patients are reflected in the figures. In all cases, the missing number of patients was approximately equivalent between the HBO_2 and NBH treatments groups. The missing data for brain tissue PO_2 and microdialysis levels were attributable to probe malfunction or placement in injured tissue such as contusion or hemorrhage. One control patient did not have ICP measurements as the ventriculostomy could not be placed because of a bilateral decompressive craniectomy. The F2-isoprostane measurements did not begin until the 19th patient. There were no statistically significant differences with respect to group characteristics (Table 2).

Twenty-seven patients (39%) had an evacuated mass lesion, and 13 (19%) had an unevacuated mass lesion (Table 3). Twenty-nine patients (42%) had diffuse brain injury with a CT scan score of II (8 patients) or III (21 patients). There were no statistically significant differences in CT entry scores among the groups, although a higher percentage of mass lesions (both evacuated and unevacuated) was seen in the HBO_2 group ($p = 0.07$). Surgical evacuation of the mass lesions generally took place before randomization.

TABLE 2: Summary of characteristics in 69 brain-injured patients

Variable	Treatment Group			Total
	HBO_2	NBH	Control	
no. of patients	26	21	22	69
M/F ratio	23:3	17:4	18:4	58:11
average age (yrs)	34	37	36	35
average entry GCS score	5.6	5.9	6.0	5.8
% w/ multiple trauma	62	48	64	58
% op mass lesions	50	38	27	39
% w/ episode of ICP hypertension	50	48	45	48

Hyperbaric O_2 Administration

The first 17 patients randomized to the HBO_2 arm were placed in a Class A, 4-lock multiplace chamber (Vacudyne, Inc.), and the next 9 were placed in a 34-inch-diameter Bara-Med XD monoplace chamber (Environmental Tectonics Corp.). Compression to 1.5 ATA occurred at a rate of 1.0 lb/in^2/min and lasted 17 minutes. The patients were kept at depth for 60 minutes and underwent decompression at the same rate. There were no statistically significant differences in any of the variables between the patients using the monoplace chamber and those using the multiplace chamber; therefore, their data were combined for further analysis.

Important baseline parameters were maintained between the pretreatment and posttreatment periods in all study arms. For the HBO_2 study arm, the patient was first transported to the hyperbaric chamber area, which can essentially function as an ICU. Once there, the baseline $PaCO_2$, PaO_2, ICP, and cerebral perfusion pressure were meticulously reestablished to baseline. The FiO_2 necessary to achieve a PaO_2 in the range of 90–130 mm Hg was established. The $PaCO_2$ was kept relatively constant at ~ 35 mm Hg. The Licox catheter brain tissue PO_2 microprobe was calibrated in the HBO_2 chamber (Integra Neurosciences). The respiratory settings were kept constant for 1 hour to establish a baseline. At that point the 1-hour pretreatment measurements were obtained. Subsequently,

TABLE 3: Marshall CT scan scores by treatment group*

Parameter	Treatment Group			Total
	HBO_2	NBH	Control	
CT Score II	4	5	27	11
CT Score III	23	38	32	31
evacuated mass lesion	50	38	27	39
unevacuated mass lesion	23	19	14	19

* All values are expressed as a percent.

the HBO_2 was administered. The 1-hour posttreatment measurements were drawn in the HBO_2 chamber. The patient was then transported back to the regular ICU where equilibrium was again established before obtaining the 6-hour posttreatment values. Bilateral myringotomies were performed in all patients.

Study Protocol

The first O_2 treatment was administered as soon as the entry criteria were met and the patient's condition was clinically stable. The mean time from injury to treatment was 19 ± 2 hours (range 11–27 hours). Subsequent treatments occurred every 24 hours. The hyperoxia treatments were given every 24 hours to study the duration of the treatment effect on cerebral metabolism and ICP. This time point was chosen because we anticipated that the treatment effect would last > 6 hours but < 24 hours.[80] Patients received 3 consecutive treatments unless they became brain dead or were consistently able to follow commands. Treatments were also stopped if the patient became medically unstable (sepsis or uncontrolled blood pressure). If a patient did not receive a treatment, the next treatment continued on schedule and the missed treatment was not rescheduled. This situation occurred only once in a patient in whom supraventricular tachycardia developed prior to a second HBO_2 treatment; the tachycardia was believed to be unrelated to the HBO_2. This patient was following commands before his third scheduled HBO_2 session. Neurosurgical procedures were generally performed prior to randomization into the study. Only 1 craniotomy for mass lesion evacuation and 6 decompressive craniectomies were performed during the actual study period. No neurosurgical procedure was performed during the 1-hour pretreatment to 6-hour posttreatment period; therefore, craniotomy did not appear to affect the overall treatment effect.

Baseline FiO_2 requirements were continuously monitored, and chest radiographs were obtained daily to screen for signs of pulmonary O_2 toxicity, pneumonia, and/or other pulmonary pathology. The P/F (PaO_2/FiO_2) ratio was also recorded. The O_2 treatments were discontinued if the FiO_2 requirement was > 50% to maintain a PaO_2 > 70 mm Hg.[79] If there were progressive chest radiography changes suggesting O_2 toxicity, treatment was temporarily discontinued. If the patient improved to the point that the FiO_2 requirement was ≤ 40%, treatments were resumed. However, if O_2 requirements again increased to an FiO_2 > 50%, treatments were permanently terminated.

Monitored Variables

Variables were measured before the initiation of therapy and for 24 hours after therapy. Baseline values were collected prior to hyperoxia treatments (Table 4). Continuously monitored outcome variables included brain tissue PO_2, ICP, microdialysate lactate, glucose, pyruvate, and glycerol. The brain tissue PO_2 measurements were downloaded onto a Dell personal computer. Mean values over each 30-minute interval were calculated, except during HBO_2 when mean values were calculated over every 15-minute interval. The highest mean 15-minute value of brain tissue PO_2 during each treatment session was recorded. Microdialysate samples were collected every hour. The recovery rate of the microdialysate was reduced during compression, so samples could not be obtained during HBO_2 sessions.[32] Intracranial pressure measurements were recorded hourly. Global metabolic measures, including CBF, $AVDO_2$, and ventricular CSF lactate, were obtained before treatment and 1 and 6 hours after every treatment. The $CMRO_2$ was calculated by multiplying the CBF by the $AVDO_2$. Measurements of O_2 toxicity, including ventricular CSF F2-isoprostane concentrations and BAL inflammatory markers (IL-8 and IL-6 assays), were taken before treatment and 6 hours after treatment. The P/F ratio was calculated and recorded before each treatment. All monitored variables were recorded in a database (Access 2003, Microsoft Corp.) and synchronized. The results of the trial allowed a direct comparison of HBO_2 and NBH in terms of their effect on the surrogate outcome variables as well as their relative toxicity. In addition, posttreatment measurements were compared with pretreatment values within each treatment arm.

TABLE 4: Baseline mean values by treatment group for measured variables prior to hyperoxia treatments*

Parameter	HBO_2	NBH	Control
CBF (ml/100 g/min)	52.0 ± 2.4	54.2 ± 3.1	55.8 ± 3.3
$AVDO_2$ (ml/dl)	4.0 ± 0.18	4.1 ± 0.23	4.4 ± 0.23
$CMRO_2$ (ml/100 g/min)	2.20 ± 0.10	2.51 ± 0.16	2.50 ± 0.13
ventricular CSF lactate (mmol/L)	2.95 ± 0.10	3.25 ± 0.18	2.44 ± 0.16
mean brain tissue PO_2 (mm Hg)	28.6 ± 1.6	29.7 ± 2.0	28.9 ± 2.1
microdialysate lactate (mmol)	2.47 ± 0.12	3.14 ± 0.21	2.93 ± 0.20
microdialysate L/P ratio	31.5 ± 1.5	30.8 ± 2.2	26.5 ± 1.6
microdialysate glycerol (μmol)	77.6 ± 6.3	140.7 ± 28.6	88.5 ± 9.2
ICP (mm Hg)	13.0 ± 0.7	11.4 ± 0.7	11.3 ± 0.8
ventricular CSF F2 isoprostane (pg/ml)	43.3 ± 2.1	48.6 ± 2.8	47.9 ± 2.2
BAL IL-6 (ng/ml)	3.11 ± 0.61	5.12 ± 1.08	6.51 ± 2.24
BAL IL-8 (ng/ml)	92.8 ± 21.5	85.3 ± 20.1	51.5 ± 8.90

* Values expressed as the means ± SEMs.

Global Cerebral Metabolism

The nitrous oxide method was used to measure CBF.[42] Arterial blood was obtained from the radial artery catheter, and jugular venous blood was drawn from the reverse internal jugular catheter inserted into the jugular bulb for the measurement of $AVDO_2$. Blood samples and ventricular CSF samples were drawn within 2 minutes of each other. Arterial and venous serum pH, PO_2, PCO_2, and O_2 saturation were measured in an i-STAT clinical portable analyzer with G3+ cartridges (Abbott Laboratories). The ventilator FiO_2 and PEEP settings were recorded every hour. The CSF was collected from the buretrol of the ventriculostomy using a sterile technique. Lactate concentrations in the ventricular CSF were immediately

assayed with an Ortho Diagnostics Vitros 950 (Ortho-Clinical Diagnostics, Inc.).

Continuous Metabolic Monitoring

A Licox catheter microprobe was used to measure brain tissue PO_2 and temperature (Integra Neurosciences). A CMA-70 microdialysis catheter was used to obtain all microdialysate samples (CMA Microdialysis). This catheter, along with the O_2 temperature probes, was inserted through the triple lumen bolt into the frontal cortex of the brain to the desired depth of 14–24 mm. No data were collected in the first 3 hours to avoid insertion artifacts. Artificial CSF solution was infused through the probes at the rate of 0.3 μl/minute. Dialysates were collected in outflow vials and frozen at −80°C. Lactate, glucose, pyruvate, and glycerol levels from the collected dialysate were measured using an offline analyzer (CMA 600 microdialysis analyzer). The L/P ratios were calculated as a marker for ischemia and the cellular redox state. Brain tissue PO_2 probes and microdialysis catheters were placed in either the right or left frontal lobe, whichever was least damaged. This location represented our "standard" or "uninjured area" of brain tissue not overtly traumatized.

Intracranial Pressure

Global ICP measurements were obtained with a tunneled intraventricular catheter. Any ICP > 15 mm Hg was treated. This treatment sequentially included mild hyperventilation, CSF drainage, osmotic agents, sedation or paralytics, and finally decompressive craniectomy. Therapeutic intensity level scores were recorded with ICP measurements.[51]

Oxygen Toxicity Markers

Bronchial alveolar lavage fluid samples were obtained through the endotracheal tube using a sterile technique and routine respiratory care. A suction catheter (Medline Industries) was wedged into a distal lung segment, and 30 ml of sterile saline (0.9% NaCl, 37°C) was instilled and then aspirated via suction into a sterile specimen collector (Allegiance Healthcare). All samples were immediately chilled at 4°C and processed within 15 minutes of collection. Samples were strained through a 60-mesh steel screen to remove mucus and were then processed in a centrifuge to remove cells, aliquoted, and frozen at −80°C until assayed for IL-8 and IL-6. The BAL IL-8 and IL-6 concentrations were determined using a commercial enzyme-linked immunosorbent assay kit per the manufacturer's instructions (BD Biosciences Pharmingen).

Cerebrospinal fluid samples taken from the buretrol of the ventriculostomy were immediately chilled at 4°C and processed within 15 minutes of collection. Samples were processed in a centrifuge to remove cells, aliquoted, and frozen at −80°C. The CSF F2-isoprostane content was measured using a commercial enzyme immunoassay kit (Cayman Chemical).

Statistical Analysis

Patient characteristics across treatment groups were compared using chi-square tests.

Outcome analyses focused on the posttreatment effects because our primary study hypothesis was that the effects of hyperoxia on cerebral metabolism and ICP occur primarily after, rather than during, treatment. A ratio of post- to pretreatment values was used to study differences among treatment groups for all tests except those for ICP, for which the difference between pre- and posttreatment values was used because of 0 values. At the same time, the actual test values were used to study differences from pre- to posttreatment within each treatment group.

A mixed-effects linear model with the fixed effects of treatment (group), time, day, and the treatment time interaction (only significant variables were kept in the final model), random patient effect, and autoregressive covariance matrix was used for testing the treatment effect. Given the skewness of the post-/pretreatment ratio, a natural log transformation was applied to all post-/pretreatment ratios. When an overall significant group or time*group interaction effect was found in the models by using the post-/pretreatment ratio, post hoc orthogonal contrasts were used to determine the between-group difference at each time point. To decrease the number of post hoc comparisons within the models that used actual test values to evaluate within-group differences from pre- to posttreatment values, the first 3 posttreatment values at 1, 2, and 3 hours were used for the continuously monitored test variables (that is, brain tissue PO_2, microdialysate, and ICP measurements).

Similar models were also fit to understand the relationship between the highest value of brain tissue PO_2 during the hyperoxia treatment and increasing or decreasing CBF, $CMRO_2$, microdialysate lactate, microdialysate L/P ratio, and ICP values. These models were run with the natural log of the post-/pretreatment ratio as the dependent variable, the highest value of brain tissue PO_2 as an independent variable, a random patient effect, and an autoregressive covariance matrix. A linear regression was used to evaluate the relationship between the highest value of brain tissue PO_2 and the P/F ratio, and the t-test was used to compare mean brain tissue PO_2 values between a P/F ratio ≥ 200 and a P/F ratio < 200. Statistical significance was set at $p < 0.05$ in all analyses, and SAS version 9.1 (SAS Institute) was used to perform all analyses.

Results

Comparisons of Cerebral Metabolism Measurements Between the Pre- and Posttreatment Periods

Cerebral blood flow was significantly elevated from the pretreatment interval to 6 hours posttreatment in patients in the HBO_2 group ($p < 0.0001$). The CBF in the NBH and control groups did not change. The HBO_2 and control groups' $AVDO_2$ significantly decreased from baseline to 6 hours after treatment ($p < 0.05$). There was no change in the $AVDO_2$ for the NBH group when the treatment periods were compared.

The $CMRO_2$ did not significantly change from pretreatment to posttreatment in any group. However, when the patients were assigned to reduced, normal, or increased

categories according to the CBF classification system developed by Obrist et al.[70] and modified by Robertson et al.,[78] significant differences were found. The $CMRO_2$ significantly increased from pretreatment to 6 hours posttreatment in patients in the HBO_2 group who had started the treatment with reduced or normal CBF ($p = 0.007$). The $CMRO_2$ also significantly increased from pretreatment to 1 hour posttreatment in the NBH patients who had started the treatment with reduced or normal CBF ($p = 0.0093$). There was no change in $CMRO_2$ for any CBF category in the control group or for the increased CBF category in the HBO_2 or NBH groups.

Ventricular CSF lactate levels significantly decreased for 6 hours after both the HBO_2 ($p = 0.045$) and NBH treatments ($p < 0.0001$). No change was seen in the control group.

When the pre- to posttreatment time periods were compared, mean brain tissue PO_2 levels were significantly increased after HBO_2 therapy for the first 3 hours posttreatment (see *Statistical Analysis*, $p < 0.001$). They were elevated for 1 hour following NBH treatment ($p = 0.0173$). There was no change in the control group.

The HBO_2 group had a significant decrease in the levels of lactate dialysate from pretreatment to 1 hour posttreatment ($p = 0.0427$). The NBH and control groups showed no changes in microdialysate lactate after each treatment period.

The microdialysate L/P ratio was significantly decreased from baseline following HBO_2 sessions for the 1- to 3-hour posttreatment time points ($p < 0.0001$). There were no changes from pre- to posttreatment in the NBH or control groups.

There were no meaningful significant changes in the levels of microdialysate glucose when time periods were compared.

Comparisons of Cerebral Metabolic Measurements Among Treatment Groups

For 6 hours after HBO_2, CBF was significantly elevated by ~ 26% as compared with that in the control group ($p = 0.0061$). The posttreatment effect was similar for all 3 days. There was no difference in CBF between the NBH and control groups. The $AVDO_2$ remained unchanged after treatment when comparing the groups. The $CMRO_2$ significantly increased by 32% as compared with that in the control group for 6 hours after HBO_2 treatments on all 3 days ($p = 0.0103$). There was no change in $CMRO_2$ after the NBH treatments as compared with those after standard care. Figure 1 shows $CMRO_2$ with post-/pretreatment ratio means.

Ventricular CSF lactate levels significantly decreased for 6 hours after both the HBO_2 and the NBH treatments compared with those following standard care ($p < 0.05$). The most robust treatment effect on ventricular CSF lactate for both the NBH and HBO_2 groups was seen on Day 1, but all 3 days followed the same pattern ($p = 0.0049$).

Brain tissue PO_2 increased during the treatment sessions in patients in the HBO_2 and NBH groups, with levels in the former group higher than in the latter. The mean baseline brain tissue PO_2 level was ~ 29 ± 4 mm Hg in all 3 treatment groups. The mean in-treatment brain tissue

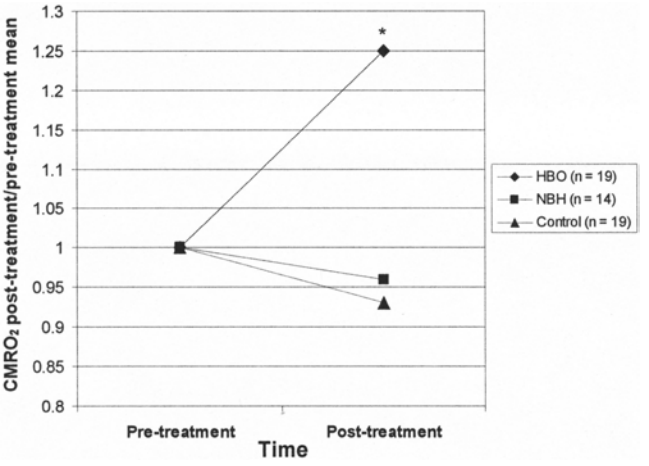

Fig. 1. Graph showing $CMRO_2$ with post-/pretreatment ratio means. A value > 1 indicates the posttreatment value is > the pretreatment value, and a value < 1 indicates the posttreatment value is < the pretreatment value. The graph also depicts the overall comparison of change among the treatment arms. There was an improvement of 32% from pre- to posttreatment in the HBO_2 group as compared with the control group (standard care). There was no change in the NBH group as compared with the control group. As a significant time*group interaction was not found in the statistical model, only the global pre- to posttreatment ratio means are shown. *$p = 0.01$, compared with the standard treatment (control) group. n = number of patients.

PO_2 values significantly increased in both the HBO_2 and NBH groups in comparison with the control group (NBH, 86 ± 12 mm Hg; and HBO_2, 223 ± 29 mm Hg; $p < 0.0001$). In comparison with levels in the control group, the mean brain tissue PO_2 values decreased to pretreatment levels for the NBH group within 1 hour after each treatment was completed. The HBO_2 treatment group's mean brain tissue PO_2 levels remained significantly higher than in the control group—by ~ 50% throughout the 20-hour posttreatment period for each of the 3 days ($p < 0.05$). Figure 2 shows brain tissue PO_2 with post-/pretreatment ratio means.

The HBO_2 patients' dialysate levels of lactate significantly decreased by 13% below control group levels for 5 hours after each treatment session was completed on all 3 days ($p = 0.0170$). The NBH group's dialysate lactate levels decreased by 7% after each treatment was completed as compared with levels in the control group; this result almost reached statistical significance ($p = 0.0835$).

The ratio of L/P levels of microdialysate were significantly decreased after treatment in both the HBO_2 and NBH groups in comparison with the control group. Microdialysate L/P ratios posttreatment were decreased by 10% in the HBO_2 group ($p < 0.0001$) and by 3% in the NBH group, compared with control group levels ($p = 0.0037$). Figure 3 shows microdialysate L/P ratios with post-/pretreatment ratio means.

There were no meaningful significant changes in the levels of microdialysate glucose when the treatment arms were compared.

Intracranial Pressure

The HBO_2 group's ICP was significantly lower than

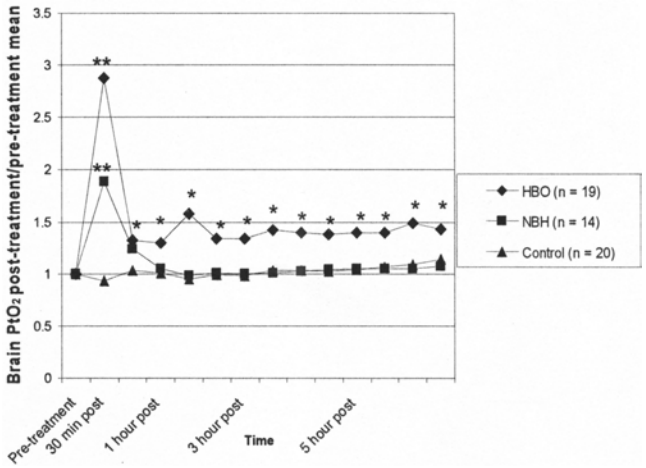

Fig. 2. Graph showing brain tissue PO_2 with post-/pretreatment ratio means. A value > 1 indicates the posttreatment value is > the pretreatment value, and a value < 1 indicates the posttreatment value is < the pretreatment value. The graph also depicts the overall comparison of change among the treatment arms. In the HBO_2 group compared with the control group, there was an increase of ~ 280% in brain tissue PO_2 from pretreatment to 30 minutes posttreatment. The HBO_2 group's brain tissue PO_2 then remained higher than that in the control group by ~ 50% throughout the posttreatment period. In comparison with the control group, the NBH group had a 180% increase in brain tissue PO_2 at 30 minutes posttreatment, but the brain tissue PO_2 decreased to baseline levels within 1 hour after each treatment was completed. Because a significant time*group interaction was found in the statistical model, the ratio means are shown for the first 6 hours posttreatment. *p < 0.05 and **p < 0.0001, compared with the control group. post = posttreatment.

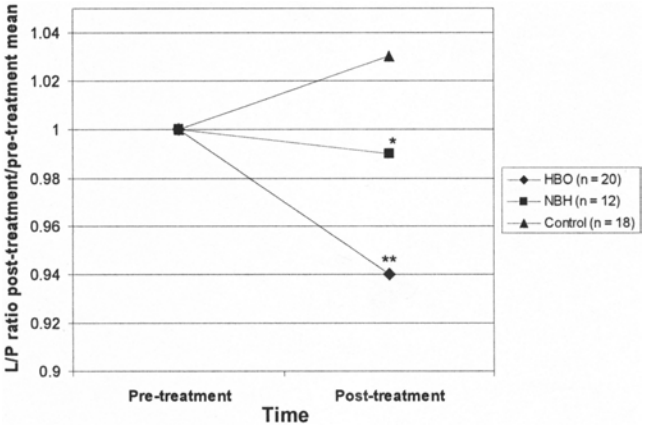

Fig. 3. Graph showing microdialysate L/P ratio in "uninjured" brain with posttreatment/pretreatment ratio means. A value > 1 indicates the posttreatment value is > the pretreatment value, and a value < 1 indicates the posttreatment value is < the pretreatment value. This figure also depicts the overall comparison of change between the treatment arms. Posttreatment microdialysate L/P ratios were decreased by 10% for patients in the HBO_2 group and by 3% for those in the NBH group, in comparison with control group levels. As a significant time*group interaction was not found in the statistical model, only the global pre- to posttreatment ratio means are shown. *p = 0.0037 and **p < 0.0001 in comparison with the control group.

that in the control group after treatment until the next treatment session (p = 0.0010). The NBH group's ICP measures did not differ significantly from those in the control group following each treatment session. Patients whose ICP was > 15 mm Hg before treatment experienced the largest decrease. The posttreatment effect was the same for all 3 days. Figure 4 shows the mean difference in ICP from pre- to posttreatment; there was no significant change for any treatment group. The TIL score significantly decreased from pre- to posttreatment for patients in the HBO_2 group as compared with the control group (p = 0.0006). There was no difference in the TIL score between the NBH and control groups.

Oxygen Toxicity

The levels of CSF F2-isoprostane did not significantly change over time for either the HBO_2 or NBH group in comparison with the controls. Neither was there a significant change for any group when the pre- to posttreatment periods were analyzed. Figure 5 shows CSF F2-isoprostane with post-/pretreatment ratio means. Levels of dialysate glycerol also stayed constant in all treatment arms. Neither HBO_2 nor NBH group levels of microdialysate glycerol differed significantly from those of the control group. The HBO_2 and NBH group BAL levels of IL-6 and IL-8 cytokines posttreatment did not significantly differ from levels in the control group or on comparison of the treatment periods.

Treatments in 2 patients in the NBH group were stopped because of increased baseline FiO_2 requirements and/or chest radiography changes. One patient had chest injuries, including lung contusion. The other patient had a history of chronic pulmonary obstructive disease, but this fact was unknown until a CT scan of the chest was obtained after completing the 1st day of treatment. There

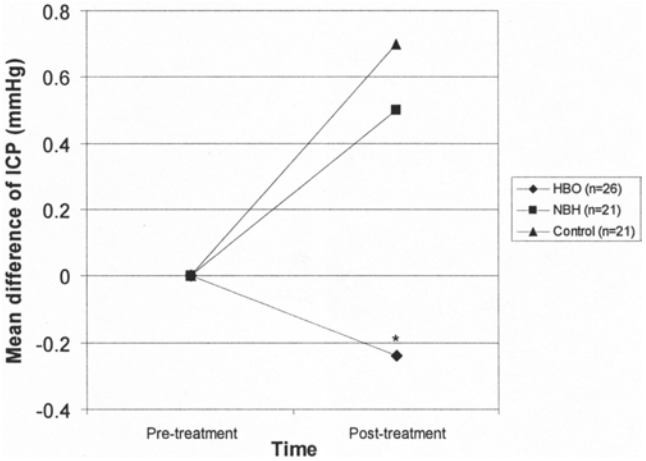

Fig. 4. Graph showing the mean pre- to posttreatment difference in ICP resulting from the statistical model. The difference in pre- to posttreatment values was used for ICP instead of the ratio of pretreatment values to posttreatment values because of 0 values. This figure also depicts the overall comparison of change between the treatment arms. The HBO group's difference in ICP from pre- to posttreatment was significantly lower than the control group. The NBH group's difference in ICP from pre- to posttreatment did not differ significantly from the control group following treatment sessions. As a significant time*group interaction was not found in the statistical model, only overall pre- to posttreatment mean differences are shown. *p = 0.0010 in comparison with the control group.

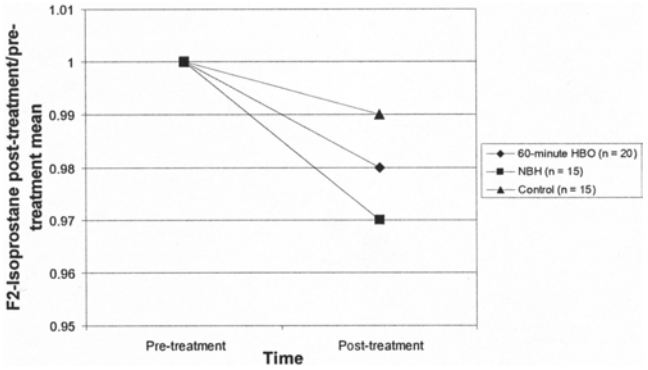

Fig. 5. Graph showing ventricular CSF F2-isoprostane with post-/pretreatment ratio means. A value > 1 indicates the posttreatment value is > the pretreatment value, and a value < 1 indicates the posttreatment value is < the pretreatment value. This graph also depicts the overall comparison of change among the treatment arms. The levels of CSF F2-isoprostane did not change over time for either the HBO_2 or NBH group in comparison with the control group. As a significant time*group interaction was not found in the statistical model, only overall pre- to posttreatment ratio means are shown.

was no increased incidence of pneumonia, FiO_2 requirement ≥ 50%, or PEEP > 10 cm H_2O for either the HBO_2 or NBH groups as compared with the control group.

Critical Level of Brain Tissue PO_2

The highest 15-minute mean value of brain tissue PO_2 during each treatment session was recorded. This value was added as an independent variable within the mixed-effects linear model for CBF, $CMRO_2$, microdialysate lactate, microdialysate L/P ratio, and ICP. Brain tissue PO_2 levels ≥ 200 mm Hg were reached in 51% of the HBO_2 treatment sessions and 5% of the NBH treatments. There was a significant improvement in each variable when the mean brain tissue PO_2 level was ≥ 200 mm Hg, regardless of the treatment arm. Patient CBF ($p = 0.0042$) and $CMRO_2$ ($p = 0.0097$) significantly increased after the treatment sessions when the brain tissue PO_2 was ≥ 200 mm Hg compared with their values when PO_2 did not reach that level. Levels of dialysate lactate ($p = 0.0012$) and the dialysate L/P ratio ($p < 0.0001$) significantly decreased after treatment when values of brain tissue PO_2 were ≥ 200 mm Hg as well. The effect of brain tissue PO_2 levels on ICP was not significant.

The P/F Ratio

The level of brain tissue PO_2 achieved during each treatment session was significantly higher when the pretreatment P/F ratio was ≥ 200 for both the HBO_2 ($p = 0.0293$) and NBH groups ($p = 0.0001$). In the HBO_2 group, the mean level of brain tissue PO_2 during treatment was 169 mm Hg when the baseline P/F ratio was < 200, compared with 244 mm Hg when the ratio was ≥ 200. During NBH treatment, the mean brain tissue PO_2 level was 49 mm Hg when the pretreatment P/F ratio was < 200 and 108 mm Hg when the ratio was ≥ 200. Furthermore, during logistic regression, the P/F ratio was a significant independent predictor of the highest level of brain tissue PO_2 achieved in both the HBO_2 and NBO treatments ($p = 0.0101$).

Discussion

This is the first report on a prospective, randomized clinical trial comparing the effect of HBO_2 versus NBH on oxidative cerebral metabolism and ICP. It also represents the first time that brain tissue PO_2 and microdialysis monitoring have been systematically performed in both monoplace and multiplace hyperbaric chamber systems. Evidence strongly suggested that a critical brain tissue PO_2 level of ≥ 200 mm Hg is required to achieve robust improvement in cerebral metabolism. Moreover, it seems important to monitor brain tissue PO_2 during O_2 therapy to achieve the appropriate O_2 level in the brain.

Investigators agree that ischemia and hypoxia are critical factors leading to secondary injury.[8,9,14,102] However, during the 1st or 2nd week after severe TBI, the presence of ischemia has been more elusive and controversial. There seem to be at least 2 reasons for this fact. First, O_2 delivery to brain tissue is impaired not only by decreased CBF but also by reduced O_2 diffusion to cells, which is not identified by CBF measurements.[53,81,89] Menon et al.[53] have used brain tissue PO_2 monitoring and images of OEFs derived from PET scanning to calculate the cerebral PvO_2. These data were used to derive a PvO_2 to brain tissue PO_2 gradient in the region of interest around the brain tissue PO_2 monitor, which provided a measure of the efficacy of microvascular O_2 delivery. Despite similar CBF reductions with hyperventilation, hypoxic regions achieved significantly smaller OEF increases compared with normoxic regions. Increased diffusion barriers appeared to reduce cellular O_2 delivery following TBI and the ability of the brain to increase O_2 extraction in response to hypoperfusion. Ultrastructural data demonstrating microvascular collapse, endothelial swelling, and perivascular edema provided a structural substrate for this abnormal physiology.[53]

The second reason relates to the fact that oxidative metabolism is markedly reduced in large regions of the brain after TBI.[15,26,100] Mitochondrial dysfunction is correlated with this hypometabolic state and may be its cause.[46,87,99,107] The $CMRO_2$ tends to be ~ 50% of normal with $AVDO_2$ showing no increased extraction of O_2 following severe TBI.[70] Similarly, PET scanning has not demonstrated increased OEFs.[26,100] Therefore, the brain is not ischemic relative to its markedly reduced metabolic demands after severe TBI. Mitochondria are dysfunctional, and oxidative metabolism is thus depressed.

Cerebral Metabolism

Studies have shown that local brain tissue PO_2 levels are significantly correlated with ischemia and outcome.[96,97,109] Van den Brink et al.[97] have demonstrated the presence of early ischemia at the tissue level with reduced initial brain tissue PO_2 and have found that a low PO_2 was an independent predictor of death and an unfavorable outcome. Stiefel et al.[90] have found that nearly one-third of aggressively treated patients with severe TBI had initial brain tissue PO_2 levels ≤ 10 mm Hg despite cerebral perfusion pressure values > 60 mm Hg. This level of cerebral tissue PO_2 is associated with a poor outcome. Hyperbaric O_2 clearly leads to a remarkable increase in the amount

of O_2 delivered to brain tissue in patients with TBI. This increase in brain tissue PO_2 not only occurs during treatment but also seems to persist after the HBO_2 treatment session is completed, as compared with the brain tissue PO_2 following NBH treatment, which decreased to baseline within 1 hour after treatment.

Data from many studies have indicated that increased CSF lactate production and elevated levels of microdialysate lactate are markers for anaerobic metabolism caused by either a lack of O_2 (ischemia) or damage to the mitochondria.[24,45,56,86,96] In addition, raised microdialysate levels of lactate probably reflect the global glycotic rate.[93,94] A continued high level of lactate in the brain has been shown to be a poor prognostic indicator after brain injury.[23,45,56,65] As in previous clinical studies demonstrating that HBO_2 reduces CSF levels of lactate,[35,61,80] data in the present study showed that both HBO_2 and NBH significantly decrease ventricular CSF lactate, indicating improved aerobic metabolism and tissue hypoxia. In addition, microdialysate lactate levels decreased significantly for 5 hours after HBO_2 treatments and tended to improve after NBH treatments in the uninjured brain, as compared with levels following standard care (controls).

The microdialysate L/P ratio is believed to be a superior marker for cerebral anaerobic metabolism and a measure of the cytoplasmic redox state that is highly specific for secondary ischemia.[73,94] It reflects the nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide ratio and the degree of aerobic metabolism.[85,108,110] No previous clinical TBI study has shown a sustained improvement in the microdialysate L/P ratio after treatment. The significant decrease in the ratio posttreatment in patients in the HBO_2 group and, to a lesser extent, in those in the NBH group indicates a shift toward a better cellular redox state after hyperoxia treatments.

Although it is only 2% of a person's body weight, the brain consumes 20% of the O_2 delivered to the body's tissues.[108] There is no O_2 storage in the brain. Under normal conditions, mitochondria consume 90% of the O_2; therefore, $CMRO_2$ is a measurement of mitochondrial metabolism. In the present study, measures of global cerebral metabolism, including CBF, $AVDO_2$, and $CMRO_2$, followed the same pattern described in previous hyperoxia clinical trials and experimental studies.[18,54,80,110] Tisdall et al.[94] have stated that if hyperoxia improves mitochondrial function and cerebral aerobic metabolism, then $CMRO_2$ will rise. Global oxidative cerebral metabolism and CBF were significantly improved (by ~ 30%) for 6 hours after HBO_2, but not after NBH treatment, as compared with levels following standard care. Cerebral blood flow and $CMRO_2$ are closely coupled and respond to cellular activity, that is, mitochondrial functional recovery. A concurrent measurement of improvement in the mitochondrial redox state further supports this finding. Experimental studies with HBO_2-treated animals have shown a simultaneous improvement in adenosine triphosphate production.[110] These data show that increased tissue O_2 delivery is capable of driving an increase in O_2 utilization, leading to improved cerebral aerobic metabolism.

Intracranial Pressure

Intracranial hypertension is the most significant cause of deterioration and death following severe TBI.[41,66] It has been a clinical axiom for decades that intractable intracranial hypertension in severe TBI is associated with a high mortality rate.[41,57,76] Hyperbaric O_2 has been shown in both experimental and clinical studies to reduce ICP[12,34,58,79,80,92] and cerebral edema after severe brain injury.[60,67,72,91] These latter studies have suggested that HBO_2 might be promoting blood-brain barrier integrity, reducing cerebral edema and hyperemia, which in turn helps to reduce the elevated ICP. Only 1 study in the literature has documented decreasing ICP following NBH treatment, which occurred after 24 hours of NBH.[95] In the present study, ICP followed the same pattern described in previous clinical trials of hyperoxia.[54,79,80,92] There was a significant decrease in ICP after HBO_2 treatment in comparison with levels following standard care. The NBH group did not demonstrate a reduction in ICP. The decrease in the TIL score indicates that ICP was treated less aggressively following the HBO_2 sessions.

Critical Level of Brain Tissue O_2

Data in this study strongly suggested that a high brain tissue PO_2 is necessary to significantly improve cerebral aerobic metabolism, particularly $CMRO_2$, which reflects mitochondrial function. When brain tissue PO_2 was ≥ 200 mm Hg, the effect was especially robust; NBH treatment induced this PO_2 level during only 5% of treatments, whereas HBO_2 attained it 51% of the time. However, the positive effects of NBH imply an incremental phenomenon of hyperoxia rather than an "all-or-nothing" effect. If brain tissue PO_2 levels ≥ 200 mm Hg had been consistently achieved, the results of our study may have been even stronger. In future clinical trials, it will be important to monitor brain tissue PO_2 during HBO_2 therapy and increase the atmospheric pressure as needed to achieve a brain tissue PO_2 ≥ 200 mm Hg in all patients with TBI.

Mechanism of HBO_2

Oxygen delivery depends on a pressure gradient from the alveolar spaces to blood and finally to brain tissue itself. Hyperbaric O_2 increases this vital O_2 delivery pressure gradient. Brain tissue PO_2 monitoring, both experimental and clinical, has recorded levels of 200–300 mm Hg with HBO_2 at 1.5 ATA.[18] Such values typically represent a 10-fold increase over baseline brain tissue PO_2 levels. Mechanistically, it is not entirely clear why the very high brain tissue PO_2 levels are achieved. However, one explanation is that HBO_2 at 1.5 ATA increases the amount of dissolved O_2 in the plasma ~ 10-fold (0.3–3.2 ml/dl).[39] There are potential significant diffusion barriers to O_2 in both the lungs and brain. In the lung, ventilator-acquired pneumonia, severe atelectasis, pulmonary contusions, and adult respiratory distress syndrome can all significantly reduce the arterial O_2 content at a given FiO_2. This phenomenon can be quantitated using the P/F ratio (that is, PaO_2/FiO_2).[82] Rosenthal et al.[82] have found that if the P/F ratio was ≤ 250, brain tissue PO_2 levels were significantly reduced during an O_2 challenge (FiO_2 of 100% for 20 minutes). The current study showed that a P/F ratio ≥ 200 was significantly correlated with higher

brain tissue PO_2 levels during the hyperoxia treatments. In fact, the P/F ratio was an independent predictor for the highest level of brain tissue PO_2 achieved during both HBO_2 and NBH treatments. The fact that a P/F ratio of 200, as opposed to 250, was the critical level in this study may relate to the ability of HBO_2 to drive the O_2 delivery pressure gradient. There are also potentially significant diffusion barriers to O_2 delivery in the brain after TBI that persist beyond 24 hours.[53] Thus, monitoring actual brain tissue PO_2 levels achieved during cerebral O_2 delivery therapy appears to be critical.

An increasing body of evidence has demonstrated the ability of nitric oxide to inhibit electron transport via cytochrome oxidase through competition with O_2 for binding.[30,62,108] Elevated tissue levels of O_2, by favorably influencing the binding of O_2 in mitochondrial redox enzyme systems, seemed to improve mitochondrial function. This improved function results in the more efficient use of baseline amounts of O_2 after HBO_2 treatment.[18,80,84,94,108] Therefore, although the treatment effect of HBO_2 in the early hours after TBI (when ischemia is most overt) is important, it is not limited to that time period. It appears to be effective in improving oxidative cerebral metabolism during a much more prolonged period of metabolic dysfunction, which lasts for days.[69,80]

A criticism of the potential of HBO_2 in the treatment of TBI is that such treatments are relatively brief and any effect is therefore transient. However, Contreras and colleagues[16] have documented that improved glucose utilization persisted for at least 24 hours after the last HBO_2 treatment in lesioned rats. Experimental studies performed at Virginia Commonwealth University have shown that the positive effects on mitochondrial function persisted for 3 hours after 60-minute HBO_2 treatments in a model of lateral fluid percussion injury in rats.[18,110] Clinically, personnel at our institution have shown that $CMRO_2$ values remain improved for 6 hours after the completion of HBO_2 treatment both in previous human studies and in the present study.[80] The positive effect of serial HBO_2 treatments on $CMRO_2$ was present for 5 days after injury. This concept is important because the HBO_2 treatments can be repeated daily to maintain their beneficial metabolic effect over many days after injury.

Oxygen Toxicity

The biomolecular basis of O_2 toxicity involves the formation of ROSs as an intermittent event in the oxidant damage to cell membranes and their components.[38] The "free radical" is defined as "a molecule with an unpaired electron in its outer orbit." Oxygen free radicals are formed during normal oxidative metabolism in all aerobic cells and are reduced within the mitochondrial cristae, as part of normal oxidative phosphorylation.[10] The degree of oxidant damage appears to be determined by a stoichiometric relationship between the rate of the formation of ROSs and their rate of metabolic elimination or "quenching" by antioxidants.[2,40] Oxygen toxicity depends on the PO_2 as well as the duration of O_2 exposure. Studies demonstrating the increased formation of ROSs and secondary lipid peroxidation in the brain have typically used HBO_2 exposure of ≥ 3.0 ATA.[33,40,68,75]

The lung is the organ most commonly damaged by hyperoxia since the O_2 tension in the surface area exposed to O_2 in the lungs is substantially higher than in other tissues.[44] The mechanism by which pulmonary injury occurs has been termed "oxidative stress."[49,105] When the inhaled O_2 exceeds the protective capacity of the autogenous antioxidants in the lungs, acute pulmonary pneumonitis characterized by 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 occurs.[19,20] The amount of these proinflammatory cytokines in BAL has been shown to be predictive of acute lung injury and pulmonary infection during exposure to increased concentrations of inspired O_2.[25,64] Oxygen toxicity can progress to alveolar and interstitial edema, alveolar hemorrhages, and proteinaceous exudates indistinguishable from acute respiratory distress syndrome. Patients who have sustained severe TBIs are prone to the development of atelectasis and ventilator-acquired pneumonia. It is difficult to distinguish the relative impact of initial lung contusion and aspiration from the possible toxicity of HBO_2 therapy. The fact that BAL levels of IL-6 and IL-8 cytokines posttreatment in the HBO_2 or NBH group did not significantly differ from those in the control group and did not demonstrate any increase from pretreatment to posttreatment strongly suggests that there was no pulmonary O_2 toxicity resulting from the treatment paradigms used in the study. In addition, there was no increased incidence of pneumonia, FiO_2 requirements > 50%, or PEEP > 10 cm H_2O for either the HBO_2 or the NBH groups as compared with the control group.

Hyperoxia can also 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.[21,22,38,71] Additionally, the brain has limited natural protection against free radicals—that is, it has limited ROS scavenging ability, has poor catalase activity, and is rich in iron, which is an initiator of ROS generation in brain injury via the Fenton reaction. The F2-isoprostanes are a unique series of prostaglandin-like compounds formed in vivo from the free radical–catalyzed peroxidation of arachidonic acid.[63] A large body of evidence has been accumulated indicating that the quantification of these products of lipid peroxidation provides a reliable marker of in vivo oxidant injury especially to cell membranes.[28,74,77] Therefore, ventricular CSF F2-isoprostane has been used to assess peroxidation in patients who have sustained a severe TBI.[4,5]

Glycerol is an end product of phospholipid degradation in neural tissue cell membranes.[27,29,55] It is a marker of cell damage whether caused by O_2 toxicity via free radical formation and lipid peroxidation or secondarily from ischemia.

Careful monitoring of ventricular CSF F2-isoprostane and microdialysate glycerol revealed no evidence of cerebral oxidative toxicity in this study. In fact, there is experimental evidence that hyperbaric oxygenation treatment induces increased ischemic tolerance by protecting against mitochondrial alterations.[103,104] This evidence implies that successive HBO_2 treatments, such as those given in this study, may have a similar effect on evolv-

ing secondary brain injury. By improving the cellular redox state, the formation of free radicals may be suppressed.[10,94]

Delivering HBO_2 at 1.5–2.0 ATA for 60 minutes, including decompression and compression intermittently 2–3 times per 24 hours, is a relatively low O_2 exposure and carries a low risk of O_2 toxicity. The UPTD (unit pulmonary toxicity dose) is a theoretical method for calculating relative O_2 doses.[3,106] One UPTD is equal to 1 minute of 100% O_2 at 1 ATA. Appropriate conversion factors, that is, multipliers of 1 minute of 100% O_2 at 1 ATA, allow one to quantitate the pressure of the O_2 exposure. In general, it is recommended that total O_2 exposure in a single treatment be limited to ≤ 615 UPTD. Extreme limitation of a single O_2 exposure is 1425 UPTD. This dose will produce a predicted 10% decrease in vital capacity in a healthy individual. Breathing 60% O_2 for 24 hours under normobaric conditions generates 374 UPTD, whereas breathing 100% O_2 for 24 hours under normobaric conditions, as described in the article by Tolias et al.,[95] is the equivalent of 1440 UPTD. This number exceeds the extreme upper limit for a single O_2 exposure. On the other hand, 3 HBO_2 treatments administered every 8 hours generates only 471 UPTD.[79] It is important to note that interruptions in O_2 exposure between treatments are known to increase O_2 tolerance and improve safety. For example, 600 UPTD/day in 2 treatment sessions has been administered for weeks with no evidence of accumulative pulmonary toxicity.[43]

Statistical Methods

Mixed-effects models, such as those used here and accomplished using the restricted maximum likelihood technique, are highly recommended for analyses in which data are obtained repeatedly but not at necessarily regular or identical times from a cohort of study participants.[101] Vespa et al.[101] have stated that mixed effects models should be used by all researchers studying interdependent serial physiological data. The mixed-effects model controls for the interrelatedness of sequential hourly values within each patient. These models take into account the differences in group sizes and correct for differences in pretreatment values when calculating significance.

Availability of HBO_2 Chambers

Several authors have noted that although HBO_2 has shown beneficial effects in animals and humans, this treatment option remains limited because of the expense and very limited availability of HBO_2 chambers.[94,95] Two types of HBO_2 delivery systems exist. One is the traditional multiple-occupancy large compartment chamber, which is designed to accommodate several patients and attendant medical personnel and has long represented the technology standard. Advantages include the abilities to treat multiple patients at one time and to offer direct patient attendance during each HBO_2 treatment. There are significant disadvantages, including the greater degree of technology and related support requirements, a larger physical plant footprint, and higher capitalization and operating costs.

An alternate delivery system is the monoplace chamber. It supports a single patient with attendance and support provided from the chamber exterior. The monoplace chamber has been used across a broad range of patient conditions to an increasing degree over the past 2 decades. Our institution has found it entirely adequate for the safe care and treatment of critically ill and ventilator-dependent patients who have sustained severe TBI and multiple injuries.[32] The major advantages of the monoplace chamber are its 1) minimal physical space footprint, 2) easy incorporation into and connection with a critical care support area, 3) minimal technology demands, 4) delivery system, which can be effectively and safely operated by existing nursing, respiratory, and standard medical support staff upon appropriate training, 5) lower capitalization and operating costs, and 6) absent risk of iatrogenic decompression sickness in the support staff. It should be emphasized that the monoplace chamber becomes an extension of the critical care environment. The cost of an HBO_2 monoplace chamber with appropriate adaptations for monitoring critically ill patients and its installation is ~ $200,000.

Potential Use of Hypothermia With HBO_2

The question arises regarding the interaction of 2 potential treatments for severe TBI, namely, hypothermia and HBO_2. At present, moderate hypothermia is used for ICP control, not neural protection (G. Clifton, personal communication). At most centers, hypothermia is induced and maintained with the Arctic Sun Temperature Management System (Medivance), which uses a cooling suit with a hydrogel surface covering 40% of the body. Cooling can be maintained outside of the ICU by using a battery system. In HBO_2 chambers pressurized with air, there would be no contraindication for continuing hypothermia during the HBO_2 treatment. From a physiological standpoint, hypothermia reduces $CMRO_2$ during treatment and tends to increase it after the session. How the 2 treatments would interact on the pathophysiology of severe TBI requires more investigation.

Conclusions

Data in this study can be summarized by the following 7 major points. 1) Hyperbaric O_2 had a significantly greater positive posttreatment effect than NBH on oxidative cerebral metabolism and ICP. 2) Although the treatment effect was not an all-or-nothing phenomenon, a critical brain tissue PO_2 level of 200 mm Hg seemed important to achieve a robust positive effect on cerebral metabolism, especially $CMRO_2$, which reflects mitochondrial function. Brain tissue PO_2 monitoring to determine O_2 delivery in the injured brain during O_2 therapy appeared to be important as well. 3) Hyperbaric O_2 had a posttreatment effect lasting at least 6 hours, which means that HBO_2 can be delivered intermittently to maintain the treatment effect over many days and reduce potential O_2 toxicity. 4) The treatment effect was as great on Day 3 as it was in the first 24 hours—that is, the treatment effect was the same after the first treatment as after the third—which implies that HBO_2 is effective in improving mi-

tochondrial function even when ischemia is not overtly present. 5) Intracranial pressure was reduced after HBO_2 treatments in comparison with levels following standard care. The decrease in the TIL score also indicated that ICP was treated less aggressively after the HBO_2 sessions. The NBH group did not demonstrate a reduction in ICP. 6) There was no evidence of cerebral or pulmonary O_2 toxicity in either the HBO_2 or NBH treatment paradigms administered. 7) Monoplace HBO_2 chambers are practical, straightforward to install, and adaptable to severe TBI care.

Disclosure

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