

# 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<sub>2</sub>) 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<sub>2</sub>, 60 minutes of HBO<sub>2</sub> 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<sub>2</sub>, microdialysis, and intracranial pressure were continuously monitored. Cerebral blood flow (CBF), arteriovenous differences in oxygen, cerebral metabolic rate of oxygen (CMRO<sub>2</sub>), 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<sub>2</sub> levels were significantly increased during treatment in both the HBO<sub>2</sub> (mean ± SEM, 223 ± 29 mm Hg) and NBH (86 ± 12 mm Hg) groups (p < 0.0001) and following HBO<sub>2</sub> until the next treatment session (p = 0.003). Hyperbaric O<sub>2</sub> significantly increased CBF and CMRO<sub>2</sub> for 6 hours (p ≤ 0.01). Cerebrospinal fluid lactate concentrations decreased posttreatment in both the HBO<sub>2</sub> and NBH groups (p < 0.05). The dialysate lactate levels in patients who had received HBO<sub>2</sub> decreased for 5 hours posttreatment (p = 0.017). Microdialysis lactate/pyruvate (L/P) ratios were significantly decreased posttreatment in both HBO<sub>2</sub> and NBH groups (p < 0.05). Cerebral blood flow, CMRO<sub>2</sub>, microdialysate lactate, and the L/P ratio had significantly greater improvement when a brain tissue PO<sub>2</sub> ≥ 200 mm Hg was achieved during treatment (p < 0.01). Intracranial pressure was significantly lower after HBO<sub>2</sub> 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<sub>2</sub> toxicity.

**Conclusions.** Hyperbaric O<sub>2</sub> has a more robust posttreatment effect than NBH on oxidative cerebral metabolism related to its ability to produce a brain tissue PO<sub>2</sub> ≥ 200 mm Hg. However, it appears that O<sub>2</sub> treatment for severe TBI is not an all or nothing phenomenon but represents a graduated effect. No signs of pulmonary or cerebral O<sub>2</sub> 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<sub>2</sub> = arteriovenous differences in oxygen; BAL = bronchial alveolar lavage; CBF = cerebral blood flow; CMRO<sub>2</sub> = cerebral metabolic rate of oxygen; FiO<sub>2</sub> = fraction of inspired oxygen; GCS = Glasgow Coma Scale; HBO<sub>2</sub> = 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<sub>2</sub>/FiO<sub>2</sub>; PvO<sub>2</sub> = partial pressure of venous oxygen; ROS = reactive oxygen species; TBI = traumatic brain injury; TIL = therapeutic intensity level; UPTD = unit pulmonary toxicity dose.

**T**RAUMATIC 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.<sup>13,47</sup> 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.<sup>47,66</sup>

## Hyperbaric O<sub>2</sub> and normobaric hyperoxia in traumatic brain injury

Although severe TBI results in marked heterogeneous structural pathology, there are common metabolic pathways leading to cellular energy failure.<sup>83,87,94,109</sup> There is evidence of ischemia in the first 24 hours after injury, resulting in decreased O<sub>2</sub> delivery that is inadequate to maintain efficient oxidative cerebral metabolism.<sup>8,9,102</sup> This metabolic state appears to trigger a marked increase in the glycolytic metabolism of glucose.<sup>6,7,37</sup> 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.<sup>7,46,87,88,99</sup> Diffusion barriers to the cellular delivery of O<sub>2</sub> develop and persist.<sup>53</sup> The degree to which cerebral oxidative metabolism is restored correlates with clinical outcome.<sup>31</sup> 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.<sup>41</sup>

In recent years there has been promising animal and clinical research in the area of hyperoxia as therapy, including HBO<sub>2</sub>, for severe TBI.<sup>18,69,72,79,80,94,95,110</sup> The use of HBO<sub>2</sub> in TBI treatment has been controversial. The availability and expense of HBO<sub>2</sub> chambers, O<sub>2</sub> toxicity, and safety concerns have been at the forefront of this controversy. In truth, complications from HBO<sub>2</sub> have been rare and reversible in our experience. Historically, HBO<sub>2</sub> has been seen as a mechanism to decrease CBF and ICP while increasing O<sub>2</sub> availability to injured brain cells.<sup>59,91,92</sup> As more sophisticated techniques have become available in both experimental and clinical TBI studies, however, HBO<sub>2</sub> appears to restore mitochondrial function by greatly increasing the O<sub>2</sub> delivery diffusion gradient, which subsequently improves cerebral aerobic metabolism after brain injury.<sup>18,80,95,109,110</sup> Clinically, HBO<sub>2</sub> has been shown to decrease mortality rates and improve functional outcome in severely brain-injured patients.<sup>1,36,79</sup>

Another method of supernormal O<sub>2</sub> delivery is increasing the FiO<sub>2</sub> to 100% at normobaric pressure. Normobaric hyperoxia therapy is a potentially attractive alternative to HBO<sub>2</sub> because of its ease of administration. Several studies have shown that as FiO<sub>2</sub> increases, there is a corresponding rise in brain tissue PO<sub>2</sub>.<sup>54,95,98</sup> In addition, microdialysate lactate decreases, which likely indicates improvement in tissue hypoxia.<sup>48,54,95</sup> 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.<sup>94</sup> In a direct comparison between HBO<sub>2</sub> and NBH in animal models of TBI, HBO<sub>2</sub> has clearly had a significantly more robust effect.<sup>72,110</sup> Zhou et al.<sup>110</sup> have shown that HBO<sub>2</sub> 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<sub>2</sub> toxicity during a prospective, randomized clinical trial comparing hyperbaric and normobaric O<sub>2</sub> 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), mid-brain 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.<sup>50</sup> 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."<sup>11</sup> 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<sub>2</sub>, NBH, and standard care. The HBO<sub>2</sub> treatment consisted of 100% FiO<sub>2</sub> delivered for 60 minutes at 1.5 ATA. The NBH treatment consisted of 100% FiO<sub>2</sub> given for 3 hours at 1.0 ATA. Standard care was the control treatment.

Twenty-six patients were randomized to the HBO<sub>2</sub> 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 <sub>2</sub> 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 <sub>2</sub> >50% &/or PEEP >10 cm H <sub>2</sub> O 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 <sub>2</sub> 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.<sup>17,52</sup> The saturation of jugular venous blood gas (SjO<sub>2</sub>) measurements for these samples were spuriously high, with an average value of 89%. Unfortunately, a higher percentage of patients in the HBO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>, CBF, and CMRO<sub>2</sub>). 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<sub>2</sub> and NBH treatments groups. The missing data for brain tissue PO<sub>2</sub> 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 pa-

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

Variable	Treatment Group			Total
	HBO <sub>2</sub>	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

tients). 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<sub>2</sub> group ( $p = 0.07$ ). Surgical evacuation of the mass lesions generally took place before randomization.

#### Hyperbaric O<sub>2</sub> Administration

The first 17 patients randomized to the HBO<sub>2</sub> arm were placed in a Class A, 4-lock multiplace chamber (Vaducyde, 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<sup>2</sup>/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<sub>2</sub> study arm, the patient was first transported to the hyperbaric chamber area, which can essentially function as an ICU. Once there, the baseline PaCO<sub>2</sub>, PaO<sub>2</sub>, ICP, and cerebral perfusion pressure were meticulously reestablished to baseline. The FiO<sub>2</sub> necessary to achieve a PaO<sub>2</sub> in the range of 90–130 mm Hg was established. The PaCO<sub>2</sub> was kept relatively constant at ~35 mm Hg. The Licox catheter brain tissue PO<sub>2</sub> microprobe was calibrated in the HBO<sub>2</sub> 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 <sub>2</sub>	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.



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the HBO<sub>2</sub> was administered. The 1-hour posttreatment measurements were drawn in the HBO<sub>2</sub> 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<sub>2</sub> 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.<sup>80</sup> 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<sub>2</sub> treatment; the tachycardia was believed to be unrelated to the HBO<sub>2</sub>. This patient was following commands before his third scheduled HBO<sub>2</sub> 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<sub>2</sub> requirements were continuously monitored, and chest radiographs were obtained daily to screen for signs of pulmonary O<sub>2</sub> toxicity, pneumonia, and/or other pulmonary pathology. The P/F (PaO<sub>2</sub>/FiO<sub>2</sub>) ratio was also recorded. The O<sub>2</sub> treatments were discontinued if the FiO<sub>2</sub> requirement was > 50% to maintain a PaO<sub>2</sub> > 70 mm Hg.<sup>79</sup> If there were progressive chest radiography changes suggesting O<sub>2</sub> toxicity, treatment was temporarily discontinued. If the patient improved to the point that the FiO<sub>2</sub> requirement was ≤ 40%, treatments were resumed. However, if O<sub>2</sub> requirements again increased to an FiO<sub>2</sub> > 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<sub>2</sub>, ICP, microdialysate lactate, glucose, pyruvate, and glycerol. The brain tissue PO<sub>2</sub> measurements were downloaded onto a Dell personal computer. Mean values over each 30-minute interval were calculated, except during HBO<sub>2</sub> when mean values were calculated over every 15-minute interval. The highest mean 15-minute value of brain tissue PO<sub>2</sub> during each treatment session was

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

Parameter	HBO <sub>2</sub>	NBH	Control
CBF (ml/100 g/min)	52.0 ± 2.4	54.2 ± 3.1	55.8 ± 3.3
AVDO <sub>2</sub> (ml/dl)	4.0 ± 0.18	4.1 ± 0.23	4.4 ± 0.23
CMRO <sub>2</sub> (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 <sub>2</sub> (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 iso-prostane (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.

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<sub>2</sub> sessions.<sup>32</sup> Intracranial pressure measurements were recorded hourly. Global metabolic measures, including CBF, AVDO<sub>2</sub>, and ventricular CSF lactate, were obtained before treatment and 1 and 6 hours after every treatment. The CMRO<sub>2</sub> was calculated by multiplying the CBF by the AVDO<sub>2</sub>. Measurements of O<sub>2</sub> 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<sub>2</sub> 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.

### Global Cerebral Metabolism

The nitrous oxide method was used to measure CBF.<sup>42</sup> 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<sub>2</sub>. Blood samples and ventricular CSF samples were drawn within 2 minutes of each other. Arterial and venous serum pH, PO<sub>2</sub>, PCO<sub>2</sub>, and O<sub>2</sub> saturation were measured in an i-STAT clinical portable analyzer with G3+ cartridges (Abbott Laboratories). The ventilator FiO<sub>2</sub> 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<sub>2</sub> and temperature (Integra Neurosciences). A CMA-70 microdialysis catheter was used to obtain all microdialysate samples (CMA Microdialysis). This catheter, along with the O<sub>2</sub> 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<sub>2</sub> 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.<sup>51</sup>

#### *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<sub>2</sub>, microdialysate, and ICP measurements).

Similar models were also fit to understand the relationship between the highest value of brain tissue PO<sub>2</sub> during the hyperoxia treatment and increasing or decreasing CBF, CMRO<sub>2</sub>, 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<sub>2</sub> 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<sub>2</sub> and the P/F ratio, and the t-test was used to compare mean brain tissue PO<sub>2</sub> 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<sub>2</sub> group (p < 0.0001). The CBF in the NBH and control groups did not change. The HBO<sub>2</sub> and control groups’ AVDO<sub>2</sub> significantly decreased from baseline to 6 hours after treatment (p < 0.05). There was no change in the AVDO<sub>2</sub> for the NBH group when the treatment periods were compared.

The CMRO<sub>2</sub> did not significantly change from pretreatment to posttreatment in any group. However, when the patients were assigned to reduced, normal, or increased

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categories according to the CBF classification system developed by Obrist et al.<sup>70</sup> and modified by Robertson et al.,<sup>78</sup> significant differences were found. The CMRO<sub>2</sub> significantly increased from pretreatment to 6 hours post-treatment in patients in the HBO<sub>2</sub> group who had started the treatment with reduced or normal CBF ( $p = 0.007$ ). The CMRO<sub>2</sub> 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<sub>2</sub> for any CBF category in the control group or for the increased CBF category in the HBO<sub>2</sub> or NBH groups.

Ventricular CSF lactate levels significantly decreased for 6 hours after both the HBO<sub>2</sub> ( $p = 0.045$ ) 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<sub>2</sub> levels were significantly increased after HBO<sub>2</sub> therapy for the first 3 hours post-treatment (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<sub>2</sub> 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<sub>2</sub> 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.

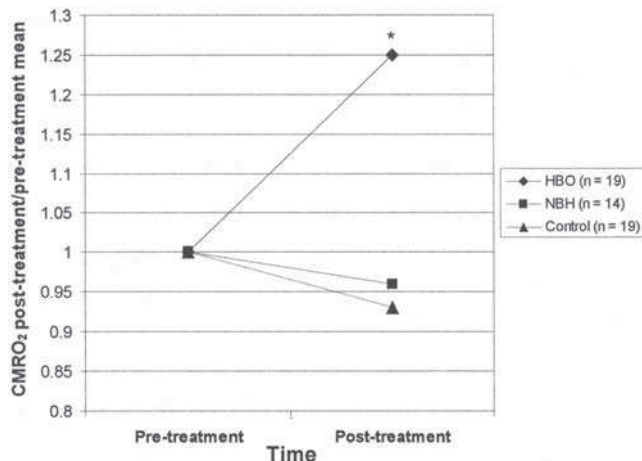
There were no meaningful significant changes in the levels of microdialysate glucose when time periods were compared.

### *Comparisons of Cerebral Metabolic Measurements Among Treatment Groups*

For 6 hours after HBO<sub>2</sub>, 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<sub>2</sub> remained unchanged after treatment when comparing the groups. The CMRO<sub>2</sub> significantly increased by 32% as compared with that in the control group for 6 hours after HBO<sub>2</sub> treatments on all 3 days ( $p = 0.0103$ ). There was no change in CMRO<sub>2</sub> after the NBH treatments as compared with those after standard care. Figure 1 shows CMRO<sub>2</sub> with post-/pretreatment ratio means.

Ventricular CSF lactate levels significantly decreased for 6 hours after both the HBO<sub>2</sub> 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<sub>2</sub> groups was seen on Day 1, but all 3 days followed the same pattern ( $p = 0.0049$ ).

Brain tissue PO<sub>2</sub> increased during the treatment sessions in patients in the HBO<sub>2</sub> and NBH groups, with levels in the former group higher than in the latter. The mean baseline brain tissue PO<sub>2</sub> level was  $29 \pm 4$  mm Hg in all 3 treatment groups. The mean in-treatment brain tissue



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

The HBO<sub>2</sub> 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 ( $p = 0.0835$ ).

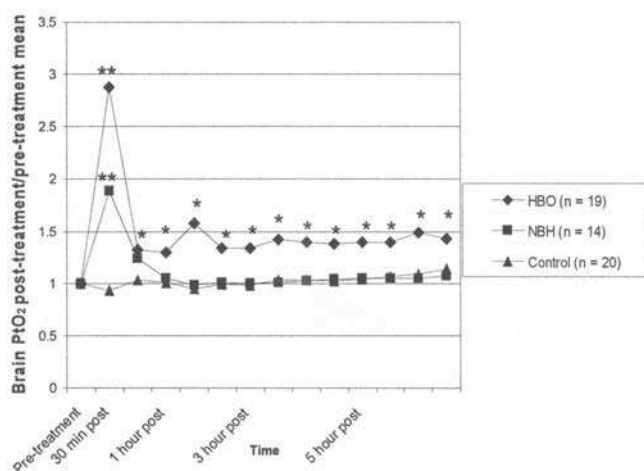
The ratio of L/P levels of microdialysate were significantly decreased after treatment in both the HBO<sub>2</sub> and NBH groups in comparison with the control group. Microdialysate L/P ratios posttreatment were decreased by 10% in the HBO<sub>2</sub> group ( $p < 0.0001$ ) and by 3% in the NBH group, 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<sub>2</sub> group's ICP was significantly lower than





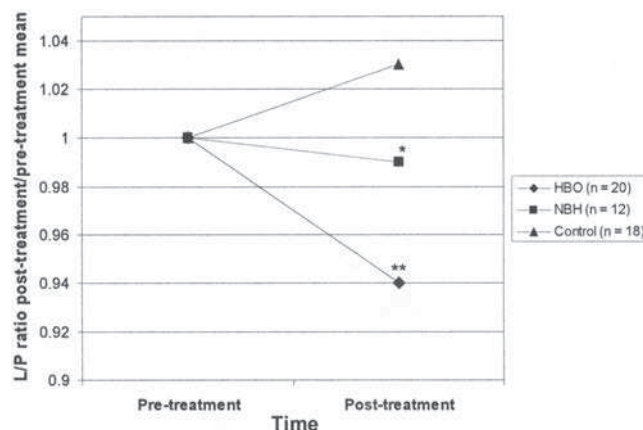
**FIG. 2.** Graph showing brain tissue PO<sub>2</sub> with post-/pretreatment ratio means. A value > 1 indicates the posttreatment value is > the pretreatment value, and a value < 1 indicates the posttreatment value is < the pretreatment value. The graph also depicts the overall comparison of change among the treatment arms. In the HBO<sub>2</sub> group compared with the control group, there was an increase of ~ 280% in brain tissue PO<sub>2</sub> from pretreatment to 30 minutes posttreatment. The HBO<sub>2</sub> group's brain tissue PO<sub>2</sub> 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<sub>2</sub> at 30 minutes posttreatment, but the brain tissue PO<sub>2</sub> 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.

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<sub>2</sub> 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*

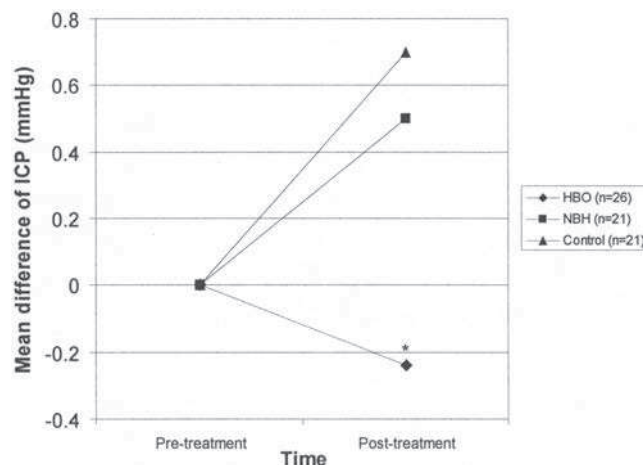
The levels of CSF F2-isoprostane did not significantly change over time for either the HBO<sub>2</sub> or NBH group in comparison with the controls. Neither was there a significant change for any group when the pre- to posttreatment periods were analyzed. Figure 5 shows CSF F2-isoprostane with post-/pretreatment ratio means. Levels of dialysate glycerol also stayed constant in all treatment arms. Neither HBO<sub>2</sub> nor NBH group levels of microdialysate glycerol differed significantly from those of the control group. The HBO<sub>2</sub> 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



**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<sub>2</sub> 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.

stopped because of increased baseline FiO<sub>2</sub> 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.

## Hyperbaric O<sub>2</sub> and normobaric hyperoxia in traumatic brain injury

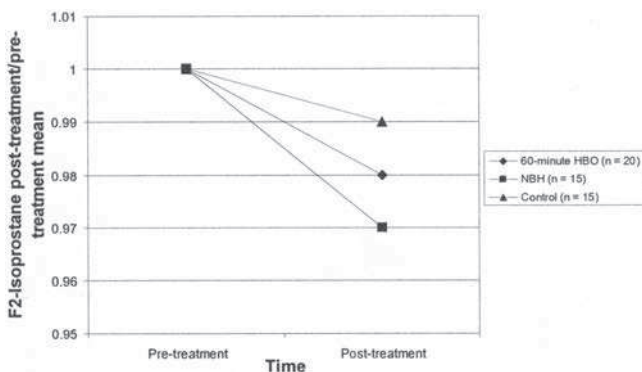


Fig. 5. Graph showing ventricular CSF F2-isoprostane with post-/pretreatment ratio means. A value > 1 indicates the posttreatment value is > the pretreatment value, and a value < 1 indicates the posttreatment value is < the pretreatment value. This graph also depicts the overall comparison of change among the treatment arms. The levels of CSF F2-isoprostane did not change over time for either the HBO<sub>2</sub> 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<sub>2</sub> requirement  $\geq$  50%, or PEEP > 10 cm H<sub>2</sub>O for either the HBO<sub>2</sub> or NBH groups as compared with the control group.

### Critical Level of Brain Tissue PO<sub>2</sub>

The highest 15-minute mean value of brain tissue PO<sub>2</sub> during each treatment session was recorded. This value was added as an independent variable within the mixed-effects linear model for CBF, CMRO<sub>2</sub>, microdialysate lactate, microdialysate L/P ratio, and ICP. Brain tissue PO<sub>2</sub> levels  $\geq$  200 mm Hg were reached in 51% of the HBO<sub>2</sub> treatment sessions and 5% of the NBH treatments. There was a significant improvement in each variable when the mean brain tissue PO<sub>2</sub> level was  $\geq$  200 mm Hg, regardless of the treatment arm. Patient CBF ( $p = 0.0042$ ) and CMRO<sub>2</sub> ( $p = 0.0097$ ) significantly increased after the treatment sessions when the brain tissue PO<sub>2</sub> was  $\geq$  200 mm Hg compared with their values when PO<sub>2</sub> 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<sub>2</sub> were  $\geq$  200 mm Hg as well. The effect of brain tissue PO<sub>2</sub> levels on ICP was not significant.

### The P/F Ratio

The level of brain tissue PO<sub>2</sub> achieved during each treatment session was significantly higher when the pretreatment P/F ratio was  $\geq$  200 for both the HBO<sub>2</sub> ( $p = 0.0293$ ) and NBH groups ( $p = 0.0001$ ). In the HBO<sub>2</sub> group, the mean level of brain tissue PO<sub>2</sub> during treatment was 169 mm Hg when the baseline P/F ratio was < 200, compared with 244 mm Hg when the ratio was  $\geq$  200. During NBH treatment, the mean brain tissue PO<sub>2</sub> level was 49 mm Hg when the pretreatment P/F ratio was < 200 and 108 mm Hg when the ratio was  $\geq$  200. Furthermore, during logistic regression, the P/F ratio was a significant independent predictor of the highest level of brain tissue PO<sub>2</sub> achieved in both the HBO<sub>2</sub> and NBO treatments ( $p = 0.0101$ ).

## Discussion

This is the first report on a prospective, randomized clinical trial comparing the effect of HBO<sub>2</sub> versus NBH on oxidative cerebral metabolism and ICP. It also represents the first time that brain tissue PO<sub>2</sub> and microdialysis monitoring have been systematically performed in both monoplace and multiplace hyperbaric chamber systems. Evidence strongly suggested that a critical brain tissue PO<sub>2</sub> level of  $\geq$  200 mm Hg is required to achieve robust improvement in cerebral metabolism. Moreover, it seems important to monitor brain tissue PO<sub>2</sub> during O<sub>2</sub> therapy to achieve the appropriate O<sub>2</sub> level in the brain.

Investigators agree that ischemia and hypoxia are critical factors leading to secondary injury.<sup>8,9,14,102</sup> 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<sub>2</sub> delivery to brain tissue is impaired not only by decreased CBF but also by reduced O<sub>2</sub> diffusion to cells, which is not identified by CBF measurements.<sup>53,81,89</sup> Menon et al.<sup>53</sup> have used brain tissue PO<sub>2</sub> monitoring and images of OEFs derived from PET scanning to calculate the cerebral PvO<sub>2</sub>. These data were used to derive a PvO<sub>2</sub> to brain tissue PO<sub>2</sub> gradient in the region of interest around the brain tissue PO<sub>2</sub> monitor, which provided a measure of the efficacy of microvascular O<sub>2</sub> 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<sub>2</sub> delivery following TBI and the ability of the brain to increase O<sub>2</sub> extraction in response to hypoperfusion. Ultrastructural data demonstrating microvascular collapse, endothelial swelling, and perivascular edema provided a structural substrate for this abnormal physiology.<sup>53</sup>

The second reason relates to the fact that oxidative metabolism is markedly reduced in large regions of the brain after TBI.<sup>15,26,100</sup> Mitochondrial dysfunction is correlated with this hypometabolic state and may be its cause.<sup>46,87,99,107</sup> The CMRO<sub>2</sub> tends to be  $\sim$  50% of normal with AVDO<sub>2</sub> showing no increased extraction of O<sub>2</sub> following severe TBI.<sup>70</sup> Similarly, PET scanning has not demonstrated increased OEFs.<sup>26,100</sup> 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<sub>2</sub> levels are significantly correlated with ischemia and outcome.<sup>96,97,109</sup> Van den Brink et al.<sup>97</sup> have demonstrated the presence of early ischemia at the tissue level with reduced initial brain tissue PO<sub>2</sub> and have found that a low PO<sub>2</sub> was an independent predictor of death and an unfavorable outcome. Stiefel et al.<sup>90</sup> have found that nearly one-third of aggressively treated patients with severe TBI had initial brain tissue PO<sub>2</sub> levels  $\leq$  10 mm Hg despite cerebral perfusion pressure values > 60 mm Hg. This level of cerebral tissue PO<sub>2</sub> is associated with a poor outcome. Hyperbaric O<sub>2</sub> clearly leads to a remarkable increase in the amount



of O<sub>2</sub> delivered to brain tissue in patients with TBI. This increase in brain tissue PO<sub>2</sub> not only occurs during treatment but also seems to persist after the HBO<sub>2</sub> treatment session is completed, as compared with the brain tissue PO<sub>2</sub> 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<sub>2</sub> (ischemia) or damage to the mitochondria.<sup>24,45,56,86,96</sup> In addition, raised microdialysate levels of lactate probably reflect the global glycolytic rate.<sup>93,94</sup> A continued high level of lactate in the brain has been shown to be a poor prognostic indicator after brain injury.<sup>23,45,56,65</sup> As in previous clinical studies demonstrating that HBO<sub>2</sub> reduces CSF levels of lactate,<sup>35,61,80</sup> data in the present study showed that both HBO<sub>2</sub> 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<sub>2</sub> 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.<sup>73,94</sup> It reflects the nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide ratio and the degree of aerobic metabolism.<sup>85,108,110</sup> No previous clinical TBI study has shown a sustained improvement in the microdialysate L/P ratio after treatment. The significant decrease in the ratio post-treatment in patients in the HBO<sub>2</sub> 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<sub>2</sub> delivered to the body's tissues.<sup>108</sup> There is no O<sub>2</sub> storage in the brain. Under normal conditions, mitochondria consume 90% of the O<sub>2</sub>; therefore, CMRO<sub>2</sub> is a measurement of mitochondrial metabolism. In the present study, measures of global cerebral metabolism, including CBF, AVDO<sub>2</sub>, and CMRO<sub>2</sub>, followed the same pattern described in previous hyperoxia clinical trials and experimental studies.<sup>18,54,80,110</sup> Tisdall et al.<sup>94</sup> have stated that if hyperoxia improves mitochondrial function and cerebral aerobic metabolism, then CMRO<sub>2</sub> will rise. Global oxidative cerebral metabolism and CBF were significantly improved (by ~ 30%) for 6 hours after HBO<sub>2</sub>, but not after NBH treatment, as compared with levels following standard care. Cerebral blood flow and CMRO<sub>2</sub> 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<sub>2</sub>-treated animals have shown a simultaneous improvement in adenosine triphosphate production.<sup>110</sup> These data show that increased tissue O<sub>2</sub> delivery is capable of driving an increase in O<sub>2</sub> utilization, leading to improved cerebral aerobic metabolism.

#### *Intracranial Pressure*

Intracranial hypertension is the most significant

cause of deterioration and death following severe TBI.<sup>41,66</sup> It has been a clinical axiom for decades that intractable intracranial hypertension in severe TBI is associated with a high mortality rate.<sup>41,57,76</sup> Hyperbaric O<sub>2</sub> has been shown in both experimental and clinical studies to reduce ICP<sup>12,34,58,79,80,92</sup> and cerebral edema after severe brain injury.<sup>60,67,72,91</sup> These latter studies have suggested that HBO<sub>2</sub> 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.<sup>95</sup> In the present study, ICP followed the same pattern described in previous clinical trials of hyperoxia.<sup>54,79,80,92</sup> There was a significant decrease in ICP after HBO<sub>2</sub> 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<sub>2</sub> sessions.

#### *Critical Level of Brain Tissue O<sub>2</sub>*

Data in this study strongly suggested that a high brain tissue PO<sub>2</sub> is necessary to significantly improve cerebral aerobic metabolism, particularly CMRO<sub>2</sub>, which reflects mitochondrial function. When brain tissue PO<sub>2</sub> was ≥ 200 mm Hg, the effect was especially robust; NBH treatment induced this PO<sub>2</sub> level during only 5% of treatments, whereas HBO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> during HBO<sub>2</sub> therapy and increase the atmospheric pressure as needed to achieve a brain tissue PO<sub>2</sub> ≥ 200 mm Hg in all patients with TBI.

#### *Mechanism of HBO<sub>2</sub>*

Oxygen delivery depends on a pressure gradient from the alveolar spaces to blood and finally to brain tissue itself. Hyperbaric O<sub>2</sub> increases this vital O<sub>2</sub> delivery pressure gradient. Brain tissue PO<sub>2</sub> monitoring, both experimental and clinical, has recorded levels of 200–300 mm Hg with HBO<sub>2</sub> at 1.5 ATA.<sup>18</sup> Such values typically represent a 10-fold increase over baseline brain tissue PO<sub>2</sub> levels. Mechanistically, it is not entirely clear why the very high brain tissue PO<sub>2</sub> levels are achieved. However, one explanation is that HBO<sub>2</sub> at 1.5 ATA increases the amount of dissolved O<sub>2</sub> in the plasma ~ 10-fold (0.3–3.2 ml/dl).<sup>39</sup> There are potential significant diffusion barriers to O<sub>2</sub> 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<sub>2</sub> content at a given FiO<sub>2</sub>. This phenomenon can be quantitated using the P/F ratio (that is, PaO<sub>2</sub>/FiO<sub>2</sub>).<sup>82</sup> Rosenthal et al.<sup>82</sup> have found that if the P/F ratio was ≤ 250, brain tissue PO<sub>2</sub> levels were significantly reduced during an O<sub>2</sub> challenge (FiO<sub>2</sub> of 100% for 20 minutes). The current study showed that a P/F ratio ≥ 200 was significantly correlated with higher

## Hyperbaric O<sub>2</sub> and normobaric hyperoxia in traumatic brain injury

brain tissue PO<sub>2</sub> levels during the hyperoxia treatments. In fact, the P/F ratio was an independent predictor for the highest level of brain tissue PO<sub>2</sub> achieved during both HBO<sub>2</sub> 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<sub>2</sub> to drive the O<sub>2</sub> delivery pressure gradient. There are also potentially significant diffusion barriers to O<sub>2</sub> delivery in the brain after TBI that persist beyond 24 hours.<sup>53</sup> Thus, monitoring actual brain tissue PO<sub>2</sub> levels achieved during cerebral O<sub>2</sub> 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<sub>2</sub> for binding.<sup>30,62,108</sup> Elevated tissue levels of O<sub>2</sub>, by favorably influencing the binding of O<sub>2</sub> in mitochondrial redox enzyme systems, seemed to improve mitochondrial function. This improved function results in the more efficient use of baseline amounts of O<sub>2</sub> after HBO<sub>2</sub> treatment.<sup>18,80,84,94,108</sup> Therefore, although the treatment effect of HBO<sub>2</sub> 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.<sup>69,80</sup>

A criticism of the potential of HBO<sub>2</sub> in the treatment of TBI is that such treatments are relatively brief and any effect is therefore transient. However, Contreras and colleagues<sup>16</sup> have documented that improved glucose utilization persisted for at least 24 hours after the last HBO<sub>2</sub> 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<sub>2</sub> treatments in a model of lateral fluid percussion injury in rats.<sup>18,110</sup> Clinically, personnel at our institution have shown that CMRO<sub>2</sub> values remain improved for 6 hours after the completion of HBO<sub>2</sub> treatment both in previous human studies and in the present study.<sup>80</sup> The positive effect of serial HBO<sub>2</sub> treatments on CMRO<sub>2</sub> was present for 5 days after injury. This concept is important because the HBO<sub>2</sub> treatments can be repeated daily to maintain their beneficial metabolic effect over many days after injury.

### *Oxygen Toxicity*

The biomolecular basis of O<sub>2</sub> toxicity involves the formation of ROSs as an intermittent event in the oxidant damage to cell membranes and their components.<sup>38</sup> 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.<sup>10</sup> 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.<sup>2,40</sup> Oxygen toxicity depends on the PO<sub>2</sub> as well as the duration of O<sub>2</sub> exposure. Studies demonstrating the increased formation of ROSs and secondary lipid peroxidation in the brain have typically used HBO<sub>2</sub> exposure of ≥ 3.0 ATA.<sup>33,40,68,75</sup>

The lung is the organ most commonly damaged by hyperoxia since the O<sub>2</sub> tension in the surface area exposed to O<sub>2</sub> in the lungs is substantially higher than in other tissues.<sup>44</sup> The mechanism by which pulmonary injury occurs has been termed “oxidative stress.”<sup>49,105</sup> When the inhaled O<sub>2</sub> 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.<sup>19,20</sup> 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<sub>2</sub>.<sup>25,64</sup> 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<sub>2</sub> therapy. The fact that BAL levels of IL-6 and IL-8 cytokines posttreatment in the HBO<sub>2</sub> 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<sub>2</sub> toxicity resulting from the treatment paradigms used in the study. In addition, there was no increased incidence of pneumonia, FiO<sub>2</sub> requirements > 50%, or PEEP > 10 cm H<sub>2</sub>O for either the HBO<sub>2</sub> 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<sub>2</sub> consumption and high content of phospholipids.<sup>21,22,38,71</sup> 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 F<sub>2</sub>-isoprostanes are a unique series of prostaglandin-like compounds formed *in vivo* from the free radical-catalyzed peroxidation of arachidonic acid.<sup>63</sup> 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.<sup>28,74,77</sup> Therefore, ventricular CSF F<sub>2</sub>-isoprostane has been used to assess peroxidation in patients who have sustained a severe TBI.<sup>4,5</sup>

Glycerol is an end product of phospholipid degradation in neural tissue cell membranes.<sup>27,29,55</sup> It is a marker of cell damage whether caused by O<sub>2</sub> toxicity via free radical formation and lipid peroxidation or secondarily from ischemia.

Careful monitoring of ventricular CSF F<sub>2</sub>-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.<sup>103,104</sup> This evidence implies that successive HBO<sub>2</sub> treatments, such as those given in this study, may have a similar effect on evolu-

ing secondary brain injury. By improving the cellular redox state, the formation of free radicals may be suppressed.<sup>10,94</sup>

Delivering HBO<sub>2</sub> 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<sub>2</sub> exposure and carries a low risk of O<sub>2</sub> toxicity. The UPTD (unit pulmonary toxicity dose) is a theoretical method for calculating relative O<sub>2</sub> doses.<sup>3,106</sup> One UPTD is equal to 1 minute of 100% O<sub>2</sub> at 1 ATA. Appropriate conversion factors, that is, multipliers of 1 minute of 100% O<sub>2</sub> at 1 ATA, allow one to quantitate the pressure of the O<sub>2</sub> exposure. In general, it is recommended that total O<sub>2</sub> exposure in a single treatment be limited to ≤ 615 UPTD. Extreme limitation of a single O<sub>2</sub> exposure is 1425 UPTD. This dose will produce a predicted 10% decrease in vital capacity in a healthy individual. Breathing 60% O<sub>2</sub> for 24 hours under normobaric conditions generates 374 UPTD, whereas breathing 100% O<sub>2</sub> for 24 hours under normobaric conditions, as described in the article by Tolia et al.,<sup>95</sup> is the equivalent of 1440 UPTD. This number exceeds the extreme upper limit for a single O<sub>2</sub> exposure. On the other hand, 3 HBO<sub>2</sub> treatments administered every 8 hours generates only 471 UPTD.<sup>79</sup> It is important to note that interruptions in O<sub>2</sub> exposure between treatments are known to increase O<sub>2</sub> 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.<sup>43</sup>

#### 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.<sup>101</sup> Vespa et al.<sup>101</sup> 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<sub>2</sub> Chambers

Several authors have noted that although HBO<sub>2</sub> has shown beneficial effects in animals and humans, this treatment option remains limited because of the expense and very limited availability of HBO<sub>2</sub> chambers.<sup>94,95</sup> Two types of HBO<sub>2</sub> 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<sub>2</sub> 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.<sup>32</sup> 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<sub>2</sub> monoplace chamber with appropriate adaptations for monitoring critically ill patients and its installation is ~ \$200,000.

#### Potential Use of Hypothermia With HBO<sub>2</sub>

The question arises regarding the interaction of 2 potential treatments for severe TBI, namely, hypothermia and HBO<sub>2</sub>. 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<sub>2</sub> chambers pressurized with air, there would be no contraindication for continuing hypothermia during the HBO<sub>2</sub> treatment. From a physiological standpoint, hypothermia reduces CMRO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> level of 200 mm Hg seemed important to achieve a robust positive effect on cerebral metabolism, especially CMRO<sub>2</sub>, which reflects mitochondrial function. Brain tissue PO<sub>2</sub> monitoring to determine O<sub>2</sub> delivery in the injured brain during O<sub>2</sub> therapy appeared to be important as well. 3) Hyperbaric O<sub>2</sub> had a posttreatment effect lasting at least 6 hours, which means that HBO<sub>2</sub> can be delivered intermittently to maintain the treatment effect over many days and reduce potential O<sub>2</sub> 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<sub>2</sub> is effective in improving mi-



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tochondrial function even when ischemia is not overtly present. 5) Intracranial pressure was reduced after HBO<sub>2</sub> 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<sub>2</sub> sessions. The NBH group did not demonstrate a reduction in ICP. 6) There was no evidence of cerebral or pulmonary O<sub>2</sub> toxicity in either the HBO<sub>2</sub> or NBH treatment paradigms administered. 7) Monoplace HBO<sub>2</sub> chambers are practical, straightforward to install, and adaptable to severe TBI care.

### Disclosure

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