Effects of hyperbaric oxygenation therapy on cerebral metabolism and intracranial pressure in severely brain injured patients

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Object. Hyperbaric oxygenation (HBO) therapy has been shown to reduce mortality by 50% in a prospective randomized trial of severely brain injured patients conducted at the authors’ institution. The purpose of the present study was to determine the effects of HBO on cerebral blood flow (CBF), cerebral metabolism, and intracranial pressure (ICP), and to determine the optimal HBO treatment paradigm.

Methods. Oxygen (100% O_, 1.5 atm absolute) was delivered to 37 patients in a hyperbaric chamber for 60 minutes every 24 hours (maximum of seven treatments/patient). Cerebral blood flow, arteriovenous oxygen difference (AVDO<sub>2</sub>), cerebral metabolic rate of oxygen (CMRO<sub>2</sub>), ventricular cerebrospinal fluid (CSF) lactate, and ICP values were obtained 1 hour before and 1 hour and 6 hours after a session in an HBO chamber. Patients were assigned to one of three categories according to whether they had reduced, normal, or raised CBF before HBO.

In patients in whom CBF levels were reduced before HBO sessions, both CBF and CMRO<sub>2</sub> levels were raised 1 hour and 6 hours after HBO (p < 0.05). In patients in whom CBF levels were normal before HBO sessions, both CBF and CMRO<sub>2</sub> levels were increased at 1 hour (p < 0.05), but were decreased by 6 hours after HBO. Cerebral blood flow was reduced 1 hour and 6 hours after HBO (p < 0.05), but CMRO<sub>2</sub> was unchanged in patients who had exhibited a raised CBF before an HBO session. In all patients AVDO<sub>2</sub> remained constant both before and after HBO. Levels of CSF lactate were consistently decreased 1 hour and 6 hours after HBO, regardless of the patient’s CBF category before undergoing HBO (p < 0.05). Intracranial pressure values higher than 15 mm Hg before HBO were decreased 1 hour and 6 hours after HBO (p < 0.05). The effects of each HBO treatment did not last until the next session in the hyperbaric chamber.

Conclusions. The increased CMRO<sub>2</sub> and decreased CSF lactate levels after treatment indicate that HBO may improve aerobic metabolism in severely brain injured patients. This is the first study to demonstrate a prolonged effect of HBO treatment on CBF and cerebral metabolism. On the basis of their data the authors assert that shorter, more frequent exposure to HBO may optimize treatment.

Key Words • hyperbaric oxygenation • brain injury • cerebral blood flow • cerebral metabolism • intracranial pressure

Rain injury continues to be a major cause of death and disability throughout the world. A prospective randomized clinical study was previously conducted at Hennepin County Medical Center to assess the effectiveness of HBO in the treatment of severely brain injured patients. A dramatic improvement in survival was shown in patients treated with HBO, but their functional recovery was not improved. Therefore, many questions persisted about the efficacy and application of HBO in cases of traumatic brain injury. One question concerned the timing of the treatments: the HBO chamber protocol in the earlier study was developed empirically, because there had been no specific recommendations in previous reports. Further investigation also was needed to elucidate the effect of HBO on cerebral metabolism, CBF, and ICP. The purpose of the present study, therefore, was to help determine the optimal HBO treatment paradigm as well as to elucidate potential metabolic effects of HBO in severely brain injured patients.

Clinical Material and Methods

Patient Population and Case Management

Thirty-seven patients treated for traumatic, severe closed-head brain injuries at the Level I Trauma Center at
Hennepin County Medical Center were entered into a prospective study to determine the effects of HBO on CBF, cerebral metabolism, and ICP. The patients' mean age was 36 ± 3 years (range 8–84 years). There were 27 male and 10 female patients. Severe brain injury was defined by assignment of a Glasgow Coma Scale score equal to or less than 8. This score was determined when no effects from paralytic agents, sedation, alcohol, and/or street drugs were present. The mean Glasgow Coma Scale score at the time of entry into the study was 5.8 ± 0.3.

To participate in the study patients also had to have a CT scan score greater than II in accordance with the classification system proposed by the Traumatic Coma Data Bank.24 Eighteen patients (49%) harbored a mass lesion (16 subdural hematomas, one epidural hematoma, and one intracerebral hemorrhage) that was evacuated. Nineteen patients (51%) had a diffuse brain injury with a CT scan score of II (four patients) or III (15 patients). Forty-six percent of the patients suffered from multiple traumas (Table 1).

Exclusion criteria included the following: 1) patients whose medical condition was not compatible with HBO therapy, such as those with an unstable pulmonary status or those who are pregnant; 2) patients having an unstable fracture that prevented their placement in the hyperbaric chamber; 3) patients under the age of 4 years, because the amount of blood required for serial measurement of CBF and serum blood assays might induce hypovolemic hypotension; and 4) patients placed in a barbiturate-induced coma during initial case management, because of the potential effects of barbiturates on cerebral metabolism.

All patients received intensive neurosurgical care that closely paralleled that of the Brain Trauma Foundation Guidelines for the Management of Severe Head Trauma. 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 ICPs greater than 15 mm Hg. In accordance with protocol all patients received prophylactic phenytoin sodium. Patient outcome was not determined because this was not an intent-to-treat study. Informed consent was obtained from the legal next of kin before the first session in the hyperbaric chamber and the protocol for this study was approved by the human subjects research committee at our institution.

### Hyperbaric Oxygenation Treatment

The first 32 patients entered into the study received HBO treatments while in a monoplace HBO chamber (Sechrist Industries, Inc., Anaheim, CA) and the last five patients while in a Class A, four-lock multiplace chamber (Vacudyne, Inc., Chicago Heights, IL). All patients received ventilation therapy throughout the entire study period. During the entire HBO treatment process, patients received 100% oxygen. Compression to 1.5 ATA occurred at a rate of 1 psi/minute and lasted 15 minutes (that is, until at depth). The patients remained in the chamber at depth for 60 minutes and the chamber was decompressed at the same rate. There were no statistically significant differences between patients treated in the monoplace and those in the multiplace chamber for any variables. Therefore, data from both groups were combined for further analysis.

The first HBO treatment was performed as soon as entry criteria were met and the patient was deemed clinically stable; the mean time from injury to initial treatment was 23 ± 2 hours (range 9–49 hours). The second treatment was given the next morning, with a minimum of 8 hours separating the two sessions. Subsequent treatments were given 24 hours apart for up to 5 more days (maximum of seven treatments/patient) or until the patient could consistently obey simple commands or was deemed brain dead. Treatments were also stopped if the patient became medically unstable due to sepsis or uncontrolled blood pressure, or if the addition of a pentobarbital-induced coma to the treatment strategy was necessary for control of ICP. The HBO treatments were performed only every 24 hours to determine if there were any prolonged effects from a session. A total of 167 HBO treatments were administered, for an average of five treatments per patient.

Patients' arterial blood pressures and electrocardiography data were monitored within the hyperbaric chamber. Bilateral myringotomies were performed in all patients. Although physical access to the patient was limited during treatment in the monoplace chamber, in an emergency the chamber could be vented in less than 10 seconds.

#### Cerebral Blood Flow

Cerebral blood flow was measured using the nitrous oxide saturation method.23 An 18-gauge Teflon catheter was inserted percutaneously into the internal jugular vein and positioned so that the tip rested in the jugular bulb. Radiographs confirmed the correct position of the catheter tip. The radial artery was cannulated. Nitrous oxide (10%) was introduced into the ventilator intake airway circuit in a stepwise fashion, and 10 timed samples of arterial and jugular venous blood were anaerobically collected during the first 16 minutes of nitrous oxide saturation. Concentrations of nitrous oxide in the blood samples were measured using an infrared analyzer (Dynatech Electro-Optics Corp., San Luis Obispo, CA) associated with an extraction system modified from that described by Swedlow and Lewis.44 The CBF was calculated on the basis of curves fit to the measured nitrous oxide concentrations and integrated to 15 minutes and to infinity. Mean CBF measured by this method in a healthy adult population is 50 ml/100 g/min.21

For each session in the hyperbaric chamber, the patient's CBF measurement before HBO was corrected for PaCO2 on the basis of a normative PaCO2 of 34 mm Hg.

### TABLE 1

<table>
<thead>
<tr>
<th>Injury</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>abdominal injury</td>
<td>6</td>
</tr>
<tr>
<td>chest injury</td>
<td>5</td>
</tr>
<tr>
<td>spine fracture</td>
<td>3</td>
</tr>
<tr>
<td>long bone fracture</td>
<td>6</td>
</tr>
<tr>
<td>joint injury</td>
<td>2</td>
</tr>
</tbody>
</table>

* Some patients had more than one injury.
and assuming a 3% change in CBF for each 1–mm Hg change in PaCO\textsubscript{2}. This value for CBF is called CBF\textsubscript{p}, and is clearly indicated as such where applicable. The corrected CBF\textsubscript{p} values before HBO were averaged across treatment sessions for each patient. The patients were then assigned to categories according to the CBF classification system developed by Obrist, et al., and modified by Robertson, et al.; that is, each patient’s mean CBF\textsubscript{p} value before HBO was compared with the normal range of CBF (32.9–55.3 ml/100 g/min). Patients with mean CBF\textsubscript{p} values two standard deviations below or above the normal range (<32.9 or >55.3 ml/100 g/min) before HBO therapy were classified as having reduced or raised CBF, respectively. Patients whose mean CBF\textsubscript{p} values were within the normal range before HBO were classified as having a normal CBF, although classifying a CBF value as normal may not necessarily mean it is physiologically appropriate for that patient.

Cerebral Metabolism

Arterial and jugular venous blood samples were obtained at the same time CBF was being measured for determination of blood gases and oxygen saturation. In each patient with an intraventricular catheter, ventricular CSF was collected for an assay of lactate concentrations. All samples were obtained 1 hour before and 1 hour and 6 hours after HBO treatment. Arterial and venous serum pH, PO\textsubscript{2}, PCO\textsubscript{2}, and oxygen saturation were measured using a radiometer (model ABL 330; Radiometer, Copenhagen, Denmark). Concentrations of CSF lactate were assayed using a glucose/lactate analyzer (model 2300 Glucose/L-Lactate analyzer; Yellow Springs Instruments, Yellow Springs, OH).

The normal AVDO\textsubscript{2} is 6.3 ml/dl.\textsuperscript{21} The CMRO\textsubscript{2}, calculated by multiplying the CBF value by the AVDO\textsubscript{2} value. The normal CMRO\textsubscript{2}, determined using this method is 3.4 ml/100 g/min.\textsuperscript{21} The CMRO\textsubscript{2} value is a positive number because there is always a net consumption of oxygen by the brain. The normal CSF lactate level ranges from 0.9 to 2 mmol/L.\textsuperscript{8}

Intracranial Pressure

The patients’ ICPs were monitored using tunneled ventriculostomy. The ICP values were recorded hourly in the neurosurgical intensive care unit and every 15 minutes during the HBO treatments. As stated earlier, an ICP higher than 15 mm Hg was treated. This treatment sequentially included hyperventilation, CSF drainage, administration of mannitol, and, finally, barbiturate therapy. A TILS for ICP management was recorded every 4 hours.\textsuperscript{5,39}

Statistical Analysis

The number of sessions in the pressurized chamber varied among patients for reasons stated earlier in Hyperbaric Oxygen Treatment. Therefore, separate ANOVAs with repeated measures were conducted for each variable (blood gasses, hemoglobin, CPP, ICP, TILS, CBF, AVDO\textsubscript{2}, CMRO\textsubscript{2}, and CSF lactate) in patients who completed seven, five, or three sessions. With the exception of AVDO\textsubscript{2} values, these analyses indicated no intrapatient variation during multiple HBO treatments. In other words, the effects of each HBO treatment did not last until the next pre-treatment measurement, and the patients reacted to each HBO treatment consistently. Therefore, ANOVAs of metabolic and physiological values were conducted for each individual session before and 1 hour and 6 hours after the session to determine any significant differences between values recorded before and after treatment. When an overall significant time effect was found, post hoc orthogonal contrasts were used to determine which specific time points differed from each other. For AVDO\textsubscript{2} values obtained for Session 1, were analyzed separately from values obtained for Sessions 2 through 7 (see Results). Averages and variances reported in Results are expressed as the means ± SEMs. Unless otherwise indicated, reported statistical findings were collected from the overall ANOVA (probability values from post hoc orthogonal comparisons are reported in the figure legends). Statistical significance was established at a probability value less than 0.05 in all analyses.

Results

Cerebral Blood Flow

Cerebral blood flow measurements were obtained in 34 patients; they were not obtained in three patients in whom inaccurate nitrous oxide measurements had been recorded by malfunctioning equipment. Five, 16, and 13 patients fell into the reduced, normal, and raised pretreatment CBF groups, respectively. Consistent with findings in other studies,\textsuperscript{20,22,32,35,36,39} patients who fell into the group with raised CBF before HBO therapy were significantly younger (mean 26 ± 3 years) than patients with normal (mean 39 ± 4 years) or reduced CBF before HBO (mean 45 ± 7 years; Pearson chi-square test, p < 0.02). The 34 patients in whom CBF was measured received 78 HBO treatments for which all CBF measurements, both before and 1 hour and 6 hours after HBO, were obtained. Cerebral blood flow was raised 1 hour and 6 hours after HBO treatment in 18 patients who began a treatment session with a reduced CBF (p = 0.001; Fig. 1). Cerebral blood flow also was raised significantly 1 hour after HBO treatment, but fell back to baseline by 6 hours posttreatment in 32 patients who began a session with a normal CBF (p = 0.049). In contrast, CBF was reduced both 1 hour and 6 hours after HBO treatment in 28 patients who began a treatment session with a raised CBF (p = 0.007). Because authors of previous reports\textsuperscript{5,10,30,37,38} have suggested that CBF is lowest during the first 24 hours after injury, the pretreatment CBF values of Session 1 were analyzed separately from pretreatment CBF values for subsequent treatment sessions. Although not statistically significant, there was a trend for the first pretreatment CBF measurement to be lower than subsequent pretreatment values (p = 0.066).

Arteriovenous Oxygen Difference

In all 37 patients AVDO\textsubscript{2} measurements were obtained. When AVDO\textsubscript{2} values across treatment sessions were compared, there was a significant difference between values for Session 1 and the rest of the sessions (Fig. 2). The AVDO\textsubscript{2} values both before and after treatment for Session 1 were higher than those for subsequent treatment ses-
sessions (p = 0.042), but the AVDO₂ values were not significantly different for Sessions 2 through 7. Therefore, for further analyses, AVDO₂ values for Sessions 2 through 7 were analyzed separately from Session 1 values.

The patients’ pretreatment AVDO₂ measurements were inversely related to their pretreatment CBF categories. The mean AVDO₂ was 5.5 ± 0.35 ml/dl in patients in the reduced CBF group, 5.1 ± 0.32 ml/dl in those in the normal CBF group, and 4.6 ± 0.22 ml/dl in those in the raised CBF group. There was also a negative correlation between patients’ averaged pretreatment AVDO₂ values and their averaged pretreatment CBF values (Pearson correlation, r = −0.398; p = 0.020).

The 37 patients in whom AVDO₂ measurements were obtained underwent 83 HBO treatments for which all pretreatment and 1- and 6-hour posttreatment AVDO₂ measurements were obtained. The HBO treatment had no effect on AVDO₂, whether it was Session 1 or Sessions 2 through 7, and regardless of pretreatment CBF values (Fig. 2).

**Cerebral Metabolic Rate of Oxygen**

Because CMRO₂ is calculated by multiplying values for CBF by those for AVDO₂ and because the CBF values were missing for three patients, CMRO₂ measurements were available for only 34 patients. These patients received 75 HBO treatments for which all pretreatment and 1- and 6-hour posttreatment CMRO₂ measurements were available. For patients who began a session with a reduced CBF, the CMRO₂ was raised both 1 hour and 6 hours after treatment (p = 0.001; Fig. 3). For patients who began a session with a normal CBF, CMRO₂ was raised significantly 1 hour after treatment, compared with pretreatment values (p = 0.033), but fell to initial levels by 6 hours after HBO. The HBO treatments had no significant effects on CMRO₂ values in patients who began a session with a raised CBF.

**Hemoglobin, Blood Gas, and CPP**

Hemoglobin, PCO₂, and pH were measured in all 37 patients. Cerebral perfusion pressure was calculated on the basis of the patient’s MABP and ICP (CPP = MABP − ICP). Each of these four measurements remained relatively constant from before treatment to both 1 hour and 6 hours after treatment, regardless of the patient’s pretreatment CBF. No statistically significant differences were found (Table 2).

**Ventricular CSF Lactate**

Secondary to difficulties obtaining some samples, ventricular CSF lactate samples were drawn in only 15 patients. These patients received 49 HBO treatments for which all pretreatment and 1- and 6-hour posttreatment CSF lactate measurements were obtained. The CSF lactate levels were decreased at 1 hour and 6 hours posttreatment when compared with pretreatment levels, regardless of the pretreatment CBF values (p = 0.011; Fig. 4). Pretreatment CSF lactate levels for individual treatment sessions were inversely related to the pretreatment CBF value, demonstrating that, in those sessions in which patients began with a reduced CBF value, CSF lactate pretreatment levels were significantly greater than those seen in sessions in which patients began with normal or raised CBF (p = 0.003). The mean CSF lactate values were...
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In the current prospective study we evaluated the effects of HBO therapy.

At some point during their stay in the intensive care unit, 44% of our patients experienced intracranial hypertension, which was defined as ICP higher than 20 mm Hg sustained for 20 or more minutes. Consistent with previous studies,10,20,35,36 most cases of intracranial hypertension developed in patients with normal and raised CBF (hypoxemia), compared with patients with reduced CBF (p = 0.038). Patients in whom intracranial hypertension developed had either diffuse cerebral swelling (CT scan score III) or an evacuated mass lesion.

The TILS did not significantly differ before and after HBO treatments, regardless of the patient’s pretreatment ICP category. This finding indicates that changes in ICP observed after the session were unlikely to be due to changes in the intensity level of other treatments used to control the patient’s ICP.

Other Variables

Although there was a wide time range from injury to treatment (9–49 hours), no significant differences in the effect of HBO on CBF, cerebral metabolism, or ICP were found between patients who began their first session within 12 or 24 hours of injury and those who did not. In addition both the type of brain injury and the types of multiple traumas did not have a significant influence on the effects of HBO therapy.

Discussion

There continues to be a long-standing debate concerning whether HBO may be potentially beneficial to severely brain injured patients. In our own institution, a prospective, randomized study of 168 patients revealed that HBO treatments reduced the mortality rate by 50%, but did not improve the rate of favorable outcome.43 Other authors have reported variable results in outcome.1,13,16,30 There have been few studies in which the mechanism of action of HBO was examined in severely brain injured patients. In the current prospective study we evaluated the effects of HBO on CBF, cerebral metabolism, and ICP to increase our understanding of its mechanism of action and also to determine the types of severely brain injured patients who would be likely to benefit from HBO treatments.

Cerebral Metabolism

A direct derivation of CBF and AVDO₂, CMRO₂ represents cerebral metabolism. In a healthy person, CBF is closely connected to, and regulated by, cerebral metabolism. If the CMRO₂ decreases, the CBF also decreases. On
the other hand, if the CMRO₂ increases, the CBF also increases. When CBF and CMRO₂ are normally metabolically coupled, the ratio between them does not change; in other words, the AVDO₂ remains constant. In severely brain injured patients, however, the CMRO₂ is typically reduced by one third to one half and only 45% of patients exhibit normal coupling of CBF and CMRO₂.

In the present study, both CMRO₂ and CBF values were raised after HBO treatments in patients who had a reduced or normal pretreatment CBF. We know of only one other clinical study in which both CMRO₂ and CBF were measured in severely brain injured patients before and after HBO treatment. In that study, CBF and CMRO₂ also were coupled after patients underwent treatment. Our study showed that AVDO₂ remained constant from before to after HBO therapy, which is also consistent with findings of previous studies. We believe, therefore, that HBO may normalize the coupling of CBF and cerebral metabolism in this subset of severely brain injured patients.

In addition to decreased cerebral metabolism, most patients with severe brain injury have increased lactate production. Many investigators believe that increased CSF lactate production indicates an anaerobic metabolic status that could be caused by either a lack of oxygen (ischemia) or damage to the mitochondria. Continued high levels of lactate in the brain have been shown to be a poor prognostic indicator after brain injury. In fact, ischemic damage has been observed in 70 to 90% of severely brain injured patients who die as a result of their injuries. Many studies involving both human and animal models have shown that severe reduction in CBF is one of the main causal factors in ischemia. In our study, hyperbaric chamber sessions in which patients had reduced pretreatment CBF values also had the highest pretreatment CSF lactate levels. This may indicate that these patients suffered from the most ischemia or had the most severe cellular dysfunction in the central nervous system.

Our study demonstrates that HBO treatments reduced CSF lactate levels, regardless of the patient’s pretreatment CBF category. This finding confirms those of previous studies of severely brain injured patients in which a decrease in CBF lactate was demonstrated either during or after HBO treatment. The increased CMRO₂ and decreased CSF lactate levels after treatment indicate that HBO may improve aerobic metabolism in severely brain injured patients. A study recently conducted by Menzel, et al., showed that increasing the FIO₂ of severely brain injured patients caused a significant increase in cerebral tissue oxygen and a decrease in cerebral tissue lactate during actual treatment. These authors also believed that these changes might indicate an improved cerebral aerobic metabolism and postulated that it may be beneficial to treat severely brain injured patients initially with 100% oxygen. They suggested that neuronal mitochondria might be damaged after severe head injury, impairing the tricarboxylic acid–cycle metabolism, which could be overridden by the mass-action effect of increased oxygen.

In the present study, HBO may have improved the ability of ischemic brain tissue or damaged mitochondria to utilize the oxygen received at baseline FIO₂ after treatment, which led to an improved posttreatment CMRO₂ and a decreased posttreatment lactate production. We hypothesize that the CBF rose in response to this increased aerobic cerebral metabolism. This trend for HBO to normalize metabolic coupling of CBF and cerebral metabolism was most apparent in patients with low pretreatment CBF and CMRO₂ and high pretreatment CSF lactate levels. Systemic factors that can influence CBF, such as...
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PCO\textsubscript{2}, CPP, hemoglobin, or blood pressure, remained relatively constant from before treatment to afterward, indicating that HBO was responsible for the changes in CBF.

In fact, findings from a recent experimental study support our theory.\textsuperscript{24} They indicate that oxygen delivered hyperbarically may influence subsequent oxygen metabolism. Using ischemic rabbit ears as the animal model, investigators found a consistent and striking increase in oxygen tension in ischemic tissue following serial HBO treatments. These investigators asserted that HBO was responsible for the changes in oxygen tissue tensions, and that these changes represented an improvement in the ability of the ischemic tissue to accept and potentially utilize oxygen.

### Intracranial Pressure

Our results indicate that ICP rose linearly during the treatment session in all patients. Originally, the mechanism of action of HBO during the session was thought to be vasoconstriction, which reduces CBF and ICP without lowering cerebral oxygenation.\textsuperscript{27,28,47} Consequently, edema and ischemia are reduced. Other authors, however, have found that HBO’s effect on ICP varies among patients and they submit that the change does not come only from cerebral vasoconstriction.\textsuperscript{13,30} We believe that ICP may rise during treatment as a result of the stimulation that occurs in the chamber. Although all the patients had undergone bilateral myringotomies and the chamber was vented, pressure in the paranasal sinuses and heat continued to increase as the session in the chamber continued, and these potentially noxious stimuli may eventually have overridden any benefit that HBO had on the patient’s ICP during treatment.

Differences could be seen, however, in patients who began the session with a low or high ICP. When the initial ICP was low (\(<15\) mm Hg), it began to rise slowly as soon as treatment started and continued to be elevated after treatment. In contrast, when the initial ICP was high (\(>15\) mm Hg), it dropped during pressurization and did not return to pretreatment levels until 30 to 45 minutes into the session. After the session was completed, the ICP again dropped below pretreatment levels. The PCO\textsubscript{2} levels were kept constant from before treatment until 6 hours after treatment.

Two previous studies\textsuperscript{5,13} demonstrated similar results when patients with elevated ICP underwent HBO treatments. During both studies, patients’ ICP decreased during the early part of the session in the hyperbaric chamber but rose as treatment continued. After the HBO treatment was completed, the patients’ ICP dropped below pretreatment levels. A third study conducted by Sukoff and Ragtz\textsuperscript{47} demonstrated that ICP decreased during the treatment session and, in most cases, remained reduced for 2 to 4 hours after the session. In that study, however, only the lowest ICP recorded during the entire treatment session was reported, rather than sequential values over time.

Our study demonstrated that patients with normal or raised pretreatment CBF suffered from intracranial hypertension more frequently than patients with reduced pretreatment CBF. All of our patients who had intracranial hypertension had either cerebral swelling or a mass lesion that had been evacuated. Raised CBF or hyperemia has been shown to be related to increased ICP, brain edema, and poor outcome.\textsuperscript{5,10,20,36,51} Obrist and colleagues\textsuperscript{16} believed that the most likely explanation for the relationship between elevated ICP and hyperemia is an increase in cerebral blood volume.

In our study, HBO lowered CBF in patients who began their chamber sessions with a raised CBF, and did so without significantly reducing their CMRO\textsubscript{2}. We also found that HBO reduced ICP in patients who had begun the session with an elevated ICP (\(>15\) mm Hg) for some time following treatment. Previous clinical studies also have confirmed this phenomenon.\textsuperscript{5,43,47} Hyperbaric oxygen may promote blood–brain barrier integrity, reducing cerebral edema and hyperemia, which in turn helps to lower elevated ICP. In fact, two experimental brain injury studies\textsuperscript{29,46} have demonstrated that both brain vascular permeability and CBF were significantly reduced in animals after HBO treatment, compared with control groups.

### Treatment Schedule

On the basis of our data we assert that shorter, more frequent sessions in the pressurized chamber (that is, 30 minutes every 8 hours) may optimize HBO treatment. The shortened time schedule is recommended because there is a rise in ICP that occurs after the patient has spent 30 minutes in the chamber, especially in patients with elevated ICP. Reduced time between treatment sessions may help sustain the positive effects of HBO on cerebral metabolism and ICP.

Previous literature\textsuperscript{3,10,32,37,38} suggests that CBF is lowest during the first 24 hours after injury. In the present study, the average time from injury to HBO treatment was approximately 24 hours. The time delay was necessary to stabilize the patients medically, to evacuate a mass lesion, to obtain informed consent from relatives, and to record pretreatment metabolic measurements. Although our data do not indicate that the time point at which HBO treatments are begun is significant, HBO did have the greatest impact in patients with reduced CBF and ischemia. This indicates that HBO therapy should be given as soon as possible after severe brain injury, when patients are at greatest risk from hypoxia and ischemia.

### Conclusions

Five major points can be summarized. 1) Our current findings of improved CMRO\textsubscript{2}, and decreased CSF lactate levels may indicate a shift toward aerobic metabolism after HBO treatment in severely brain injured patients, especially in those with reduced CBF or with ischemia. 2) Hyperbaric oxygenation appears to normalize the coupling of CBF and cerebral metabolism. 3) To our knowledge, this is the first study demonstrating that HBO therapy exerts a persistent effect on CBF and cerebral metabolism in severely brain injured patients. 4) Elevated levels of ICP and CBF were reduced after HBO treatment. 5) On the basis of our data we assert that shorter, more frequent sessions in a pressurized chamber may optimize HBO treatment.

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