Hyperbaric oxygen in the treatment of elevated intracranial pressure after head injury.

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This study is the first to evaluate the effect of hyperbaric oxygen (HBO) on elevated intracranial pressure (ICP) after severe head injury during documented controlled ventilation, hypocapnea, and minute-by-minute ICP data collection. We studied the effect of HBO at 2 atmospheres absolute (ATA) with 100% O2, on ICP in 2 patients, aged 5 and 21 years. Each patient had diffuse cerebral swelling after blunt trauma and after a gun shot wound, respectively. Both required controlled hyperventilation, osmotic diuretics and ICP monitoring. ICP, mean arterial blood pressure, pulse and atmospheric pressure were recorded at 1-min intervals during 1-hour treatments and for 15 min before and after HBO therapy. Controlled hyperventilation was continued during HBO therapy and PCO₂ was measured at intervals. Each patient underwent 4 treatments. Data was divided into 5 phases, all at 100% O2; (1) prior to therapy; (2) during pressurization from 1 to 2 ATA; (3) at 2 ATA; (4) during depressurization from 2 to 1 ATA, and (5) after HBO therapy. During pressurization the mean ICP dropped from 13 to 8 Torr, rising to 14 Torr during HBO therapy at 2 ATA, and to 16 Torr during depressurization to 1 atmosphere, then returning to 12 Torr after HBO therapy. We conclude from this preliminary work that HBO may lower ICP in head-injured patients with diffuse cerebral swelling during the first 15 min, or pressurization phase, of therapy. However, rebound elevations in ICP may occur during or after treatment. No lasting effects of treatment were seen after concluding therapy. The effect of HBO on elevated ICP has not yet been clarified, but deserves further careful study in those patients with severe enough injury to require ICP monitoring.

PMID: 3270048 [PubMed - indexed for MEDLINE]
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% O2, 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 (AVDO2), cerebral metabolic rate of oxygen (CMRO2), 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 CMRO2 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 CMRO2 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 CMRO2 was unchanged in patients who had exhibited a raised CBF before an HBO session. In all patients AVDO2 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 CMRO2 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.

PMID: 11235943 [PubMed - indexed for MEDLINE]
Comment on:


**Effects of hyperbaric oxygenation.**

- **Sukoff MH.**

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% O2, 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 (AVDO2), cerebral metabolic rate of oxygen (CMRO2), 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 CMRO2 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 CMRO2 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 CMRO2 was unchanged in patients who had exhibited a raised CBF before an HBO session. In all patients AVDO2 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 CMRO2 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.

PMID: 11565887 [PubMed - indexed for MEDLINE]
Effects of hyperbaric oxygen therapy on cerebral oxygenation and mitochondrial function following moderate lateral fluid-percussion injury in rats.

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OBJECT: In the current study, the authors examined the effects of hyperbaric O2 (HBO) following fluid-percussion brain injury and its implications on brain tissue oxygenation (PO2) and O2 consumption (VO2) and mitochondrial function (redox potential). METHODS: Cerebral tissue PO2 was measured following induction of a lateral fluid-percussion brain injury in rats. Hyperbaric O2 treatment (100% O2 at 1.5 ata) significantly increased brain tissue PO2 in both injured and sham-injured animals. For VO2 and redox potential experiments, animals were treated using 30% O2 or HBO therapy for 1 or 4 hours (that is, 4 hours 30% O2 or 1 hour HBO and 3 hours 100% O2). Microrespirometer measurements of VO2 demonstrated significant increases following HBO treatment in both injured and sham-injured animals when compared with animals that underwent 30% O2 treatment. Mitochondrial redox potential, as measured by Alamar blue fluorescence, demonstrated injury-induced reductions at 1 hour postinjury. These reductions were partially reversed at 4 hours postinjury in animals treated with 30% O2 and completely reversed at 4 hours postinjury in animals on HBO therapy when compared with animals treated for only 1 hour. CONCLUSIONS: Analysis of data in the current study demonstrates that HBO significantly increases brain tissue PO2 after injury. Nonetheless, treatment with HBO was insufficient to overcome injury-induced reductions in mitochondrial redox potential at 1 hour postinjury but was able to restore redox potential by 4 hours postinjury. Furthermore, HBO induced an increase in VO2 in both injured and sham-injured animals. Taken together, these data demonstrate that mitochondrial function is depressed by injury and that the recovery of aerobic metabolic function may be enhanced by treatment with HBO.

PMID: 15352608 [PubMed - indexed for MEDLINE]
Hyperbaric oxygen reduces blood-brain barrier damage and edema after transient focal cerebral ischemia.

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- Siebing DA,
- Sun L,
- Heiland S,
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BACKGROUND AND PURPOSE: Hyperbaric oxygen (HBO) has been shown to protect the brain parenchyma against transient focal cerebral ischemia, but its effects on the ischemic microcirculation are largely unknown. We examined the potential of HBO to reduce postischemic blood-brain barrier (BBB) damage and edema. METHODS: Wistar rats and C57/BL6 mice underwent occlusion of the middle cerebral artery (MCAO) for 2 hours. Forty minutes after filament introduction, animals breathed either 100% O2 at 3.0 atmospheres absolute (ata; HBO group) or at 1.0 ata (control) for 1 hour in an HBO chamber. In rats, MRI was performed 15 minutes after MCAO and after 15 minutes and 3, 6, 24, and 72 hours of reperfusion. In mice, BBB permeability for sodium fluorescein was measured after 24-hour reperfusion. RESULTS: Increased BBB permeability on postcontrast T1-weighted (T1w) images had a biphasic pattern. HBO reduced volumes and intensity of enhancement. Mean abnormal enhancing volumes were 71+/-10 mm3 (control) versus 47+/-10 mm3 (HBO) at 15 minutes; 111+/-21 mm3 versus 69+/-17 mm3 3 hours; 147+/-44 mm3 versus 83+/-21 mm3 6 hours; 150+/-37 mm3 versus 89+/-14 mm3 24 hours; and 322+/-52 mm3 versus 215+/-21 mm3 72 hours (all P<0.05). Interhemispheric quotients of mean gray values on T1w were at 1.73+/-0.11 versus 1.57+/-0.07 15 minutes; 1.74+/-0.07 versus 1.60+/-0.06 at 3 hours; 1.77+/-0.07 versus 1.62+/-0.06 at 6 hours; 1.79+/-0.10 versus 1.60+/-0.05 at 24 hours; and 1.81+/-0.10 versus 1.62+/-0.07 at 72 hours (all P<0.05). HBO-treated mice had significantly lower postischemic BBB permeability than mice treated with either normobaric hyperoxia or room air. Vasogenic edema assessed on T2w images and histologic sections was significantly lower in HBO-treated rats. CONCLUSIONS: Intraischemic HBO therapy reduces early and delayed postischemic BBB damage and edema after focal ischemia in rats and mice.

PMID: 16020761 [PubMed - indexed for MEDLINE]
Hyperbaric oxygen induces rapid protection against focal cerebral ischemia.

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BACKGROUND AND PURPOSE: The timing and mechanisms of protection by hyperbaric oxygen (HBO) in cerebral ischemia have only been partially elucidated. We monitored the early in vivo effects of HBO after 2 h transient focal ischemia using repetitive MRI. METHODS: Wistar rats underwent filament occlusion of the middle cerebral artery (MCAO). 40 min after MCAO, rats were placed in a HBO chamber and breathed either 100% O(2) at 3.0 atmospheres absolute (ata; n = 24) or at 1.0 ata (control; n = 24) for 1 h. Diffusion, perfusion and T2-weighted MR-images were obtained after 15 min and 3, 6 and 24 h of reperfusion. In 6 axial MR slices, volume of abnormal diffusion and T2w signals were measured in the ischemic hemisphere. Furthermore, hemispheric mean apparent diffusion coefficient- (ADC) and T2 values were calculated for statistical analysis. RESULTS: HBO significantly reduced volume of abnormal DWI signal beginning immediately after reperfusion (control: 92 +/- 28 mm(3); HBO: 64 +/- 17) and lesion size on T2w (control: 375 +/- 91 mm(3); HBO: 225 +/- 39) after 24 h. Correspondingly, mean ADC levels were lower and T2 values higher in the ischemic hemisphere in the control group. HBO reduced histological infarct size at 24 h. CONCLUSION: High-dose intraischemic HBO therapy has an immediate protective on the brain which is superior to normobaric oxygen.

PMID: 15777761 [PubMed - indexed for MEDLINE]
The potential neuroprotective effects of hyperbaric oxygen (HBO) were tested in an embolic model of focal cerebral ischemia with partially spontaneous reperfusion. Rats (n = 10) were subjected to embolic middle cerebral artery occlusion (MCAO) and diffusion weighted MRI (DWI) was performed at baseline, 1, 3, and 6 h after MCAO to determine the ADC viability threshold yielding the lesion volumes that best approximated the 2,3,5-triphenyltetrazolium chloride (TTC) infarct volumes at 24 h (experiment 1). For assessment of neuroprotective effects, rats were treated with 100% oxygen at 2.5 atmospheres absolute (ATA, n = 15) or normobaric room air (n = 15) for 60 min beginning 180 min after MCAO (experiment 2). DWI-, perfusion (PWI)- and T2-weighted MRI (T2WI) started within 0.5 h after MCAO and was continued 5 h, 24 h (PWI and T2WI only), and 168 h (T2WI only). Infarct volume was calculated based on TTC-staining at 24 h (experiment 1) or 168 h (experiment 2) post-MCAO. ADC-lesion evolution was maximal between 3 and 6 h. In experiment 2, the relative regional cerebral blood volume (rCBV) of both groups showed similar incomplete spontaneous reperfusion in the ischemic core. HBO reduced infarct volume to 145.3 +/- 39.6 mm3 vs. 202.5 +/- 58.3 mm3 (control, P = 0.029). As shown by MRI and TTC, HBO treatment demonstrated significant neuroprotection at 5 h after embolic focal cerebral ischemia that lasted for 168 h.

PMID: 16814772 [PubMed - indexed for MEDLINE]
Hyperbaric oxygen preconditioning induces neuroprotection against ischemia in transient not permanent middle cerebral artery occlusion rat model.

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OBJECTIVE: This study was designed to determine if repeated hyperbaric oxygen (HBO) exposure induces ischemic tolerance in focal cerebral ischemia.

METHODS: Sixty male SD rats were used in this study. Thirty animals underwent transient middle cerebral artery occlusion (MCAO) and the other thirty permanent MCAO model. The rats were randomly allocated to 3 sub-groups: control group (n = 10), HBO-3 group (n = 10), and HBO-5 group (n = 10). The animals in HBO-3 and HBO-5 groups received 1 hour hyperbaric oxygenation at 2.5 atmosphere absolute (ATA) in 100% oxygen every day for 3 and 5 days, respectively. The animals in the control group received sham treatments. 24 hours after the last HBO, transient MCAO (120 min) and permanent MCAO were induced by introducing a 3-0 nylon monofilament suture through internal carotid artery based on the Koizumi technique. The neurological outcome was evaluated until 24 hours after reperfusion in transient MCAO rats and ischemia in permanent MCAO rats. The infarct volume was then assessed by TTC staining.

RESULTS: In transient MCAO rats, the neurological outcome in both the HBO-3 and HBO-5 groups was better than that of the control group (P < 0.05 and 0.001). The infarct volume decreased from 171.5 +/- 113 mm3 to 40.6 +/- 49.9 mm3(P < 0.05) in the HBO-3 group and 16.2 +/- 28.8 mm3(P < 0.01) in the HBO-5 group. There were no significant differences in neurological outcome and infarct volume among the three groups in permanent MCAO rats.

CONCLUSIONS: The present study demonstrated that HBO preconditioning can induce ischemic tolerance in transient not permanent MCAO rats in a "dose-dependent" manner.

PMID: 11776082 [PubMed - indexed for MEDLINE]
Reduced infarct volume and differential effects on glial cell activation after hyperbaric oxygen treatment in rat permanent focal cerebral ischaemia.

- **Gunther A**
- **Kuppers-Tiedt L**
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Permanent middle cerebral artery occlusion (MCAO) causes neurodegeneration and a robust activation of glial cells primarily in sensorimotor brain regions of rats. It has been shown that hyperbaric oxygen (HBO) increases oxygen supply to ischaemic areas and reduces neuronal cell loss. The effects of HBO treatment on microgliosis and astrogliosis in permanent cerebral ischaemia have not been addressed so far, but might be critical for neurodegeneration and neuroprotection, respectively. Therefore, we used spontaneously hypertensive rats with permanent MCAO to investigate the time window to start HBO and to compare the effects of different HBO treatment frequencies on infarct volume and on differences with regard to microgliosis and astrogliosis. Seven days after MCAO the infarct volume was calculated from Nissl-stained brain sections by image analysis. HBO significantly decreased the infarct volume when used as early as 15, 90 or 180 min post-MCAO by 24%, 16% and 13%, respectively, in the single-treatment group. Repetitive HBO treatment (first HBO session 90 min after MCAO) was not effective. Microglial cells and astrocytes were detected by cytochemical fluorescent labelling and confocal laser scanning microscopy. In the single-treatment group we observed significantly higher astrocyte immunoreactivity but decreased microglial density in the peri-infarct region. These effects of HBO treatment on glial cells were not present in rats where HBO did not reduce the infarct volume (360 min after MCAO). Our data indicate that HBO-induced suppression of microgliosis and aggravated response of astrocytes might contribute to the reported beneficial effects of early HBO treatment in cerebral ischaemia.

PMID: 15978027 [PubMed - indexed for MEDLINE]
Therapeutic window for use of hyperbaric oxygenation in focal transient ischemia in rats.

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BACKGROUND AND PURPOSE: Hyperbaric oxygenation (HBO) is an attractive procedure that has been used frequently in cerebral ischemia. However, depending on the model of cerebral ischemia and HBO protocol, different and conflicting results were obtained in the past. This study was undertaken to reevaluate the effects of single administration of HBO in 2 models of acute cerebral ischemia: transient or permanent focal ischemia in rats. A comparison of the 2 ischemia models was undertaken to search for a putative therapeutic window. METHODS: The intraluminal middle cerebral artery occlusion model (MCAO) was used. The effect of single HBO therapy (3 atm absolute, 60 minutes) on transient or permanent focal ischemia, when applied at different times (3, 6, or 12 hours) after MCAO, was investigated; infarct volume and neurological deficits were assessed at 24 hours and up to 7 days. RESULTS: HBO had neuroprotective effects on transient MCAO when HBO was initiated within the first 6 hours, while it aggravated the ischemic injury histologically and clinically when initiated 12 hours after MCAO. In permanent MCAO, HBO did not reduce tissue damage regardless of the timing of therapy. CONCLUSIONS: HBO is highly efficient in reducing infarct volume and improving neurobehavioral outcome in transient MCAO within the first 6 hours. HBO at later time points (≥12 hours) is harmful by increasing infarct volume. In permanent MCAO, HBO failed to improve infarct volume and clinical outcome.

PMID: 14715976 [PubMed - indexed for MEDLINE]
Hyperbaric Oxygen After Global Cerebral Ischemia in Rabbits Reduces Brain Vascular Permeability and Blood Flow

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Abstract

Background and Purpose Hyperbaric oxygen (HBO) has been advocated as a therapy to improve neurological recovery after ischemia, since HBO may improve tissue oxygen delivery. We examined the effect of HBO treatment after global cerebral ischemia on early brain injury.

Methods Rabbits were subjected to 10 minutes of global cerebral ischemia by cerebrospinal fluid compression. After 30 minutes of reperfusion, rabbits either were subjected to HBO for 125 minutes and then breathed 100% O₂ at ambient pressure for 90 minutes or breathed 100% O₂ for 215 minutes. At the end of reperfusion and 90 minutes after exposure, brain vascular permeability and cerebral blood flow were measured. Somatosensory evoked potentials were monitored throughout the experiment.

Results HBO treatment reduced (P<.05) brain vascular permeability by 16% in gray matter and by 20% in white matter. Cerebral blood flow was lower (P<.05) in the HBO group (40.9±1.9 mL/min per 100 g, mean±SEM) compared with controls (50.8±2.0 mL/min per 100 g). Somatosensory evoked potential recovery was similar in the two groups (P>.05).

Conclusions HBO administered after global cerebral ischemia promoted blood-brain barrier integrity. HBO treatment also reduced cerebral blood flow; this effect was not associated with a reduction in evoked potential recovery. Since neurological outcome after global cerebral ischemia is generally poor and treatment options are limited, HBO should be further investigated as a potential therapy.

Key Words: blood-brain barrier • cerebral blood flow • hyperbaric oxygenation • somatosensory evoked potentials • rabbits
Introduction

The restoration of an adequate oxygen supply is a critical factor for brain recovery after cerebral ischemia. After ischemia, brain blood flow is heterogeneous, with regions of high flow adjacent to areas of low flow. Hyperbaric oxygen (HBO) therapy has been advocated as a method to improve tissue oxygen delivery, especially to areas of diminished flow. It has been suggested that HBO can enhance neuronal viability by its ability to increase the amount of dissolved oxygen in the blood without significantly changing blood viscosity. Furthermore, HBO may have other beneficial effects, such as reducing brain edema after injury without impairing tissue oxygen delivery.

The ability of HBO to improve neurological recovery after cerebral injury is controversial, as studies in both animals and humans have yielded conflicting results. Some of the discrepancy in the results of these studies is due to the fact that the investigations vary widely in the time after insult at which HBO was administered, many depths and durations of exposure have been used, and most studies have not had adequate controls. In addition, although there has been interest in the use of HBO after traumatic brain injury or stroke, only a few investigations have examined the effect of HBO on brain damage after global ischemia. Because there are differences in the pathophysiology of focal and global ischemia, the efficacy of HBO may also be influenced by the specific insult. A recent investigation in our laboratory suggested that HBO may improve brain recovery after global ischemia when given immediately after the insult.

The purpose of this study was to examine the effect of HBO administered after global ischemia on early brain injury. We used a rabbit model of global cerebral ischemia and a compression protocol designed to be clinically relevant and clinically feasible. Brain injury was evaluated with somatosensory evoked potential (SEP) recovery and with measurements of cerebral blood flow (CBF) and vascular permeability. We hypothesized that HBO would improve evoked potential recovery and reduce brain edema but not alter CBF.

Materials and Methods

The experimental protocol was reviewed by the institutional animal care and use committee and was certified as conforming to the principles described in the National Institutes of Health Guide for the Care and Use of Laboratory Animals (Department of Health and Human Services publication 86-23). This preparation is a modification of that described by Marshall et al. and has been used previously in our laboratory. After an overnight fast, male New Zealand White rabbits weighing 3.1 to 4.6 kg were initially anesthetized with 5% halothane in oxygen and then maintained with chloralose (50 mg/kg IV) and urethane (100 mg/kg IV as needed). An endotracheal tube was placed through a tracheostomy, and the rabbits were mechanically ventilated for the duration of the experiment. Bilateral femoral arterial and venous lines were inserted by surgical cutdown. These lines were used to monitor blood pressure, sample blood for measurement of arterial pH, PCO2, PO2, and hematocrit, and administer fluids and drugs. Body temperature was monitored with a rectal probe and maintained at 39.5±0.5°C. After the animal was positioned in a stereotaxic frame, electrodes were placed to measure SEPs
(NIC CA 1000, Nicolet Biomedical Instruments) over the right cerebral cortex with stimulation of the left median nerve (stimulus 10 to 17 mA, duration 100 microseconds, 1.7 repetitions per second, band-pass filters 30 to 3000 Hz, average of 40 repetitions). Before ischemia, five baseline SEPs were obtained, and the P1 to N1 amplitudes were averaged. SEP recovery is expressed as a percentage of this baseline value. Subsequently, an 18-gauge blunt-tipped spinal needle was inserted percutaneously in the subarachnoid space at the base of the brain to measure intracranial pressure and to infuse Elliott's B solution, a mock cerebrospinal fluid.\textsuperscript{13} Prior to ischemia, the rabbits were paralyzed with pancuronium bromide (0.1 mg/kg IV initially and as needed).

Cerebral ischemia was achieved by infusing the warmed (39°C) Elliott's B solution into the subarachnoid space so that intracranial pressure was equal to mean arterial pressure. Reperfusion was initiated by allowing the cerebrospinal fluid to drain until the intracranial pressure was less than 20 mm Hg. A cerebral perfusion pressure of at least 50 mm Hg was maintained during reperfusion by supporting the blood pressure as needed with fluid boluses and an epinephrine infusion.

Before the start of the experiment, rabbits were randomly selected to breathe either HBO or 100% oxygen at 1 atmosphere absolute after ischemia. All rabbits were subjected to 10 minutes of cerebral ischemia beginning at the time at which the SEP was undetectable. For the first 30 minutes after ischemia, animals in both groups breathed room air at ambient pressure. At the end of this period, the HBO rabbits were compressed to a depth of 2.8 atmospheres absolute where they breathed five cycles of oxygen and air, each for 20 and 5 minutes, respectively. This compression profile is a modification of US Navy Treatment Table 6.\textsuperscript{14} Decompression occurred in the last minute of the fifth air breathing period, after which the rabbits were maintained on 100% oxygen at ambient pressure for an additional 90 minutes. Control animals breathed 100% oxygen at 1 atmosphere absolute for an equivalent period of 215 minutes.

CBF was measured at the end of the 240-minute reperfusion period with \textsuperscript{[14]C]iodoantipyrine autoradiography.\textsuperscript{15} Fifty µCi/kg of \textsuperscript{[14]C]iodoantipyrine was administered over 1 minute, while aliquots of arterial blood were collected every 5 seconds for the determination of the concentration curve. After the isotope was infused, rabbits were immediately killed with T-61 euthanasia solution (Behring Diagnostics Inc), and brains were removed and frozen in isopentane at -60°C. Autoradiography was subsequently performed on 20-µm sections with Kodak SB-5 film. Optical density was measured using a photodensitometer with a 1-mm aperture in specific right and left brain regions by a technician who was blinded to treatment group. For each region, three measurements were made on three different sections, and the densities then were averaged. CBF was calculated using the concentration curve and the densitometry data. In an additional two animals, CBF was measured during the ischemic period.

Brain vascular permeability was assessed with Evans blue fluorescence according to the method of Saria and Lundberg.\textsuperscript{16} Thirty minutes before the end of the experiment, 3 mL/kg of a 2% solution of Evans blue in saline was given intravenously. Evans blue fluorescence was measured on the 20-µm sections used for autoradiography with a transmission fluorescence microscope (Carl Zeiss) equipped with a 100-W mercury lamp, BP 546, FT 580, and LP 590 filters, and a photometry computer program (Carl Zeiss). Relative intensity was determined at 540 nm after calibration with an area that had maximal intensity. Triplicate measurements were made and then averaged in each area of left and right cortical gray and left and right subcortical white matter.
Statistical analysis was performed using a PC-based software package (SOLO, version 3.0, BMDP Statistical Software). Group comparisons of physiological variables and SEP recovery were made with a repeated-measures ANOVA. CBF and Evans blue fluorescence data were analyzed with a three-factor (treatment group, right/left, brain region) ANOVA. Post hoc testing used the Student-Newman-Keuls test. All other data were analyzed with a Student's t test, except for the comparison of time from when the intracranial pressure equaled mean arterial pressure until the SEP was undetectable. The Mann-Whitney test was used for this analysis because the group variances were unequal. A value of $P<.05$ was considered significant. Data are expressed as mean±SEM.

**Results**

Twenty-two rabbits completed the experimental protocol without incident, 11 in each group. Selected physiological variables are listed in the Table 1. Group comparisons were made at six time points corresponding to specific events in the dive profile of the HBO group. These were at baseline before ischemia, 10 minutes after ischemia, early compression (10 minutes after compression/40 minutes after ischemia), mid compression (10 minutes after the start of the fourth oxygen breathing period/115 minutes after ischemia), early decompression (15 minutes after decompression/170 minutes after ischemia), and at the end of the experiment. Intracranial pressure was similar between the two groups ($P=.15$) and was less than 10 mm Hg for all animals during reperfusion. As expected, PaO$_2$ during compression in the HBO group was significantly higher ($P=.0009$) compared with control; however, these values reflect only a relative hyperoxia and not the absolute PaO$_2$ because of limitations of the blood gas analyzer at extremely high PaO$_2$s. PaO$_2$ at early decompression was higher in the HBO group ($P<.05$) and may have reflected inadequate equilibration after HBO, since the groups did not differ ($P>.05$) at the end of reperfusion. Overall pH for the HBO group (7.33±0.01) was statistically lower ($P=.015$) than that of the control group (7.37±0.01), but the groups did not differ at any one time point because the group-time interaction was not statistically significant ($P=.25$). There was no difference ($P>.05$) between the groups for the other physiological variables.

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The time from when intracranial pressure equaled mean arterial pressure until the SEP was undetectable did not differ ($P=.51$) between the two groups. These times were 2.0±0.6 minutes for the HBO animals and 1.2±0.3 minutes for the control rabbits.

Evans blue fluorescence in gray and white matter was lower ($P=.017$) in the HBO group compared with the control group (Fig 1). This indicates that animals treated with HBO had a more intact blood-brain barrier than the control rabbits, since intensity is directly proportional to vascular permeability.
CBF was measured in five brain regions: cerebral cortex, caudate/putamen, hippocampus, thalamus, and subcortical white matter. The blood flow data are displayed in Fig 2. There was no difference ($P=.54$) between blood flow in the right and left hemispheres, so these measurements were combined. Brain blood flow in the HBO group (group mean, 40.9 mL/min per 100 g) was lower ($P=.003$) than that of the control group (50.8 mL/min per 100 g) over all the regions, but there was no interaction between experimental group and brain region ($P=.75$). No CBF was detected during ischemia.

Fig 3 illustrates SEP recovery after ischemia. Evoked potentials were acquired every 10 minutes during reperfusion. Evoked potential recovery was not statistically different ($P=.13$) between the two groups over the entire reperfusion period. When examining SEP recovery from the point of initiation of HBO, the groups also were similar (mean SEP, 32.7±3.2% in the HBO group versus 25.6±3.2% in the control group; $P=.13$). Final SEP recovery was higher in the HBO group (41.4±6.0%) compared with controls (34.6±4.7%), but these values were not statistically different ($P=.53$).
Discussion

We examined the effect of HBO on early brain injury after global cerebral ischemia. In an effort to provide a clinically relevant protocol, HBO was administered after a brief delay to account for the time needed for transfer to an HBO chamber. In addition, the control animals breathed oxygen rather than room air, since it is likely that a patient would breathe an oxygen-enriched mixture after resuscitation. We found that HBO decreased brain vascular permeability and reduced postischemic brain blood when measured 90 minutes after the exposure had ended.

HBO has previously been shown to increase or not alter the blood-brain barrier in uninjured animals, but no investigation had examined the direct effect of HBO on the blood-brain barrier after global cerebral ischemia. An increased permeability with HBO might have been expected in our study, since free radicals have been implicated in the breakdown of the blood-brain barrier after ischemia. In one investigation, polyethylene-conjugated superoxide dismutase and catalase administered to piglets before ischemia blunted the increase in vascular permeability observed after 2 hours of reperfusion. Since HBO has been shown to increase the amount of free radicals generated in tissues, an increased disruption of the blood-brain barrier might have been expected with HBO treatment. Nonetheless, we observed a reduction in vascular permeability after 4 hours of reperfusion. Our results suggest that if there were any detrimental effects of free radical generation with HBO, they were outweighed by the beneficial effects of HBO.

The actual mechanism by which HBO enhanced blood-brain barrier integrity is undefined. Takahashi et al speculated that HBO acts to restore ion pump function, whereas Contreras et al demonstrated that HBO improves postischemic cerebral metabolism. Ultimately, by increasing the amount of dissolved oxygen in the blood, HBO may act by improving tissue oxygen delivery. However, the independent effects of pressure cannot be excluded.

The effect of HBO treatment on the blood-brain barrier was modest, with a reduction of vascular permeability of 16% in gray matter and 20% in white matter. We assessed blood-brain barrier integrity early in reperfusion. Whether a more pronounced effect would be observed with a longer period of reperfusion will need to be investigated.

The precise mechanism of the increase in vascular permeability after cerebral ischemia and reperfusion is unknown, although roles for opening of the interendothelial tight junctions and pinocytotic transport have been advocated. We measured permeability at a time when the tight junctions are reportedly intact, making it unlikely that the reduction in Evans blue extravasation in the HBO group resulted from a reduced CBF.

We demonstrated a reduction in CBF 4 hours after ischemia in the HBO animals, but the implication of this finding is unclear. Interpretation of measurements of CBF is dependent on the time after ischemia at which the blood flow was measured. Immediately after global ischemia, there is an short, initial hyperemia followed by a period of
hypoperfusion. The duration of this postischemic hypoperfusion crudely relates to the severity of the insult, but its importance in relation to recovery remains unknown. After about 3 hours, CBF generally increases, with a second hyperemia observed within 24 hours after ischemia. It has been suggested that the magnitude of this later increase inversely correlates with the severity of brain injury. This theory is supported by the observation that, in patients resuscitated after cardiac arrest, those with severe neurological damage had higher CBF within 24 hours after resuscitation compared with those who regained consciousness. Our results of a reduced CBF at 4 hours in the rabbits treated with HBO may be indicative of a less severely injured brain. This would be consistent with our finding of a more intact blood-brain barrier in these animals.

Alternatively, it could be argued that the reduction in CBF is harmful for brain recovery. Although we did not directly measure hemoglobin and oxygen saturation, it is likely that brain oxygen delivery in the HBO group at 4 hours after ischemia was lower than that in the control group, since the hematocrit and PaO₂ in the groups were similar at the time of CBF measurement. Nonetheless, even though tissue oxygen delivery may have been reduced at 4 hours, we did not observe a decline in SEP recovery, and the CBF values obtained were well above those reported to be detrimental to brain recovery. These issues will require further investigation.

There are other factors that could account for the reduced CBF in the HBO rabbits. Generally, cerebral oxygen delivery is matched to oxygen consumption by changes in CBF, but several factors can alter this relationship. The cerebral perfusion pressure, PaCO₂, and hematocrit can independently influence brain blood flow, but these variables were similar in the two groups and do not explain the lower CBF in the HBO group. Anesthetic agents can also affect CBF, but the animals in each group received the same agents and similar doses of drugs. Because elevations of PaO₂ are associated with cerebral vasoconstriction, the reduced CBF could be due to high tissue levels of oxygen that persisted after HBO. However, in rats treated with HBO at 4 atmospheres absolute, the time after decompression for brain tissue to reach 95% of the baseline PO₂ was 18.6 minutes. Since we measured blood flow 90 minutes after decompression, brain tissue PO₂ was not likely to be elevated in the HBO group.

Other investigations have demonstrated that HBO decreases CBF in uninjured animals and humans; however, the reduction in flow was evident only during the exposure, and blood flow returned to the baseline level within the first 15 minutes after decompression. Furthermore, breathing 90% oxygen after compression did not alter the reestablishment of CBF to precompression levels. In our study, we noted a decrease in CBF after the HBO exposure. Only two previous investigations have examined the effect of HBO on CBF in the injured brain. Using animals subjected to a dural freeze lesion, Miller et al measured CBF during compression and found that regional blood flow was reduced by 19% during HBO. CBF was not evaluated after exposure. In another study, brain blood flow was measured before and about 2 hours after HBO treatment in five comatose, head-injured patients. HBO did not alter CBF, although there was a long delay in the initiation of treatment after injury, ranging from 5 to 20 days from the onset of coma.

Few studies have examined the effect of HBO on brain recovery after global cerebral ischemia. Kapp et al subjected cats to 5 minutes of ischemia produced by occluding the ascending aorta and vena cava and found that animals treated with HBO for 2.5 hours had a significantly shortened electroencephalographic recovery time and a lower cerebrospinal fluid lactate level compared with controls ventilated with oxygen at
ambient pressure. Takahashi et al. showed that dogs treated with HBO after 15 minutes of global ischemia had improved survival and neurological outcome at 14 days when compared with untreated controls. These investigators also reported that HBO used in combination with nicardipine accelerated neurological recovery. However, Ruiz et al. could not demonstrate an improved neurological outcome at 7 days after 12 minutes of ischemia and HBO therapy. An important difference between these investigations is that in their studies, Takahashi et al. treated the animals with HBO on three separate occasions after ischemia, whereas Ruiz et al. used a single treatment early in reperfusion. Furthermore, Ruiz et al. used HBO in combination with hemodilution and magnesium infusion.

We used the amplitude of the SEP as an index of brain injury. Although there has been some controversy regarding the correlation of SEP improvement with neurological recovery, recent clinical studies indicate that SEPs have prognostic utility. In addition, this measurement has proved useful in the controlled laboratory setting where SEP recovery has been shown to correlate with the extent of cortical ischemia and brain metabolism. Our inability to demonstrate an improved electrophysiological recovery with HBO may be related to a type II error, since the power to detect a 50% increase in SEP recovery at 4 hours was 0.70 ($\alpha$=0.05). In a previous study, we demonstrated that in rabbits treated with HBO immediately after reperfusion SEP recovery at 75 minutes after ischemia was twice that of control animals ventilated with room air at ambient pressure.

HBO reduced brain vascular permeability and CBF after global ischemia without altering SEP recovery. Our study suggests that HBO may be useful to promote integrity of the blood-brain barrier after global ischemia. This effect of HBO may prove the most valuable in the treatment of patients, since there are few therapies available that have been shown to reduce postischemic vascular permeability. However, it is uncertain whether the reduction in blood flow after HBO represents an improved outcome or would be detrimental to recovery. Because neurological recovery after global ischemia is generally unsatisfactory and treatment options are limited, HBO should be further investigated as a potential therapy. Additional animal investigations should be performed to determine the optimal compression regimen and to examine long-term neurological recovery with HBO treatment.

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Footnotes

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