



## STROKE LITERATURE

Neurol Res. 2008 May;30(4):389-93.

### **Effect of large dose hyperbaric oxygenation therapy on prognosis and oxidative stress of acute permanent cerebral ischemic stroke in rats.**

**Xue L, Yu Q, Zhang H, Liu Y, Wang C, Wang Y.**

**OBJECTIVE:** To evaluate the therapeutic effect and the oxidative stress effect of 9 and 18 hour hyperbaric oxygenation therapy (HBOT) protocols on the earliest stage of acute permanent middle cerebral artery occlusion (MCAO) in rats. **METHODS:** The permanent MCAO model of rats was used. The animals were randomly divided into 9 and 18 hour HBOT groups, as well as a control group. **MAIN OUTCOME MEASURES:** (1) The Garcia neurological grading system was used to assess the therapeutic effect of hyperbaric oxygenation therapy; (2) the infarct volume was calculated with the 2,3,5-triphenyltetrazolium chloride (TTC) pathologic staining and NIH Image J software 24 and 120 hours after MCAO; (3) the level of reactive oxygen species determined by superoxide dismutase (SOD), malondialdehyde (MDA) and nitric oxide (NO) in ischemic brain tissue were separately examined at the 18, 48 and 120 hour post-ischemia time points using spectrophotometry. **RESULTS:** (1) There were significant improvements in the neurobehavioral outcome of the rats in the 9 and the 18 hour groups, as compared with rats from the control group ( $p<0.01$ ); (2) cerebral infarct volume decreased 63-64% in the rats of 9 hour group and 51-66% in the 18 hour group at the 24 and 120 hour time points, as compared with that of the control group; (3) the SOD levels of the 9 and 18 hour groups were remarkably lower than those of control group after both 18 and 48 hours ( $p<0.01$  and  $p<0.05$ ); (4) the MDA level of the 9 and 18 hour groups were both remarkably lower than the control groups, especially at 18 hours ( $p<0.05$ ). Meanwhile, the MDA level in the 9 hour group was remarkably lower than both the 18 hour group and the control group ( $p<0.01$  and  $p<0.05$ ); (5) the level of NO in both hyperbaric oxygenation therapy groups were remarkably higher than that of the control at 18 and 48 hour time points ( $p<0.01$ ). While the level in 18 hour group was remarkably lower than that of 9 hour group at 18 hour time point ( $p<0.05$ ). At the 120 hour mark, the NO levels were basically the same in all the three groups. **CONCLUSIONS:** (1) The two protocols of large dose hyperbaric oxygenation therapy are highly efficient in reducing infarct volume and improving neurobehavioral outcome in permanent MCAO rats within the earliest stages of stroke; (2) increased duration of hyperbaric oxygenation therapy does not appear to equate to improved outcomes; in fact, the longer duration may aggravate the oxidative stress in ischemic tissue.



## STROKE LITERATURE

Undersea Hyperb Med. 2008 Mar-Apr;35(2):113-29.

**Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats.**

**Yang YJ, Wang XL, Yu XH, Wang X, Xie M, Liu CT.**

**BACKGROUND AND PURPOSE:** Studies suggest that after brain injury, hyperbaric oxygen (HBO<sub>2</sub>) is neuroprotective by stimulating cell proliferation. We examine whether HBO<sub>2</sub> promotes neural stem cells (NSC) to proliferate and differentiate in neonatal hypoxic-ischemic (HI) rats. **METHODS:** Seven-day-old rat pups were subjected to unilateral carotid artery ligation followed by 2 hours of hypoxia (8% O<sub>2</sub>). HBO<sub>2</sub> was administered (2 ATA (atmospheres absolutes), once daily for 7 days) within 3 hours after HI. The proliferating neural stem cells in the subventricular zone (SVZ) and dentate gyrus (DG) were dynamically examined by 5-bromo-2-deoxyuridine (BrdU)/nestin immunofluorescence. Nestin protein was detected by western blot analysis at various time points (from 6 hours to 14 days) after HI. The migrating NSC were examined by BrdU/doublecortin (DCX) immunofluorescence 7 and 14 days after HI. The phenotype of the newborn cells was identified by BrdU/beta-tubulin, BrdU/ glial fibrillary acidic protein (GFAP) and BrdU/O4 (oligodendrocyte marker) immunofluorescence. Myelin basic protein (MBP) was examined by immunohistochemistry and pathological changes of the brain tissue were detected 28 days after HI. **RESULTS:** In neonatal HI rats treated with HBO<sub>2</sub>, the proliferation of endogenous NSC was observed in the SVZ and DG. Cell numbers peaked 7 days after HI and proliferating NSC migrated to the cerebral cortex at 14 d after HI. Twenty-eight days after HI, an increase in newly generated neurons, oligodendrocytes and MBP was observed in the HBO<sub>2</sub> group compared to the untreated and HI-treated rats. **CONCLUSIONS:** This study suggests that HBO<sub>2</sub> treatment may promote neurogenesis of the endogenous NSC in neonatal HI rats, contributing to repair of the injured brain.



## STROKE LITERATURE

Stroke. 2008 Mar;39(3):1000-6. Epub 2008 Jan 31.

### **Hyperbaric oxygen reduces tissue hypoxia and hypoxia-inducible factor-1 alpha expression in focal cerebral ischemia.**

**Sun L, Marti HH, Veltkamp R.**

**BACKGROUND AND PURPOSE:** The usefulness of hyperbaric oxygen (HBO) and normobaric hyperoxia in acute ischemic stroke is being reexplored because both improve outcome in experimental cerebral ischemia. However, even the basic mechanisms underlying oxygen therapy are poorly understood. We investigated the effect of both oxygen therapies on tissue hypoxia and on the transcription factor hypoxia-inducible factor-1 alpha. **METHODS:** Mice were subjected to filament-induced middle cerebral artery occlusion for 2 hours. Twenty-five minutes after filament introduction, mice breathed normobaric air, normobaric 100% O<sub>2</sub> (normobaric hyperoxia), or 100% O<sub>2</sub> at 3 ata (HBO) for 95 minutes. Hypoxic regions were mapped on tissue sections after preischemic infusion of the in vivo hypoxia marker EF-5. Hypoxia-inducible factor-1 alpha protein was measured after 2-hour middle cerebral artery occlusion using immunofluorescence and immunoblotting. Vascular endothelial growth factor expression was analyzed using in situ mRNA hybridization. **RESULTS:** Severity of ischemia did not differ among groups. HBO (35.2±10.4 mm<sup>2</sup>) significantly reduced the area of EF-5-stained hypoxic regions in focal cerebral ischemia compared with normobaric hyperoxia (46.4±11.2 mm<sup>2</sup>) and air (49.1±8 mm<sup>2</sup>), P<0.05, analysis of variance). Topographically, EF-5 fluorescence was decreased in medial striatum and in cortical ischemic border areas. Immunohistochemistry and immunoblotting revealed lower hypoxia-inducible factor-1 alpha protein in the ischemic hemisphere of HBO-treated mice. Moreover, mRNA in situ hybridization showed lower expression of vascular endothelial growth factor in HBO and normobaric hyperoxia groups. **CONCLUSIONS:** Measurement of extrinsic and intrinsic markers of hypoxia revealed that HBO improves penumbral oxygenation in focal ischemia. Modification of the transcription factor hypoxia-inducible factor-1 alpha and its downstream targets may be involved in effects of HBO.

## STROKE LITERATURE

Cerebrovasc Dis. 2008;25(3):193-201. Epub 2008 Jan 23.

**Neuroprotection by oxygen in acute transient focal cerebral ischemia is dose dependent and shows superiority of hyperbaric oxygenation.**

**Eschenfelder CC, Krug R, Yusofi AF, Meyne JK, Herdegen T, Koch A, Zhao Y, Carl UM, Deuschl**

The neuroprotective effect of oxygen after acute stroke in rats has been shown previously. However, the question of optimal dosing still remains unanswered. Thus, we investigated the use of oxygen at different concentrations by either normobaric oxygenation (NBO) or hyperbaric oxygenation (HBO) at different pressures in a model of transient ischemia/reperfusion in rats. Animals underwent 90 min of middle cerebral artery occlusion (MCAO) followed by 90 min of reperfusion before oxygen treatment. Oxygen was applied either by NBO (100% O<sub>2</sub>; 1.0 absolute atmosphere, ATA) or HBO (100% O<sub>2</sub>; 1.5, 2.0, 2.5 or 3.0 ATA) for 1 h. Primary endpoints were infarct volume and clinical outcome measured 24 h and 7 days following the MCAO. A statistically significant and long-lasting reduction in infarct volume was seen in the HBO 2.5 ATA and 3.0 ATA groups over a period of 7 days. The reduced infarct volume was accompanied with a statistically significant improvement in clinical outcome in the high-dose oxygen-treated groups. The presented data indicate that oxygen is a highly neuroprotective molecule in transient focal cerebral ischemia in rats, when applied early and at high doses. The effect is dose dependent and shows a superiority of HBO over NBO, when the primary endpoints infarct volume reduction and clinical outcome are analyzed. These data are important for the development of new acute stroke treatment studies in humans.

Neurobiol Dis. 2008 Jan;29(1):1-13. Epub 2007 Jul 28.

**The hyperbaric oxygen preconditioning-induced brain protection is mediated by a reduction of early apoptosis after transient global cerebral ischemia.**

**Ostrowski RP, Graupner G, Titova E, Zhang J, Chiu J, Dach N, Corleone D, Tang J, Zhang JH.**

We hypothesized that the brain-protective effect of hyperbaric oxygen (HBO) preconditioning in a transient global cerebral ischemia rat model is mediated by the inhibition of early apoptosis. One hundred ten male Sprague-Dawley (SD) rats (300-350 g body weight) were allocated to the sham group and three other groups with 10 min of four-vessel occlusion, untreated or preconditioned with either 3 or 5 hyperbaric oxygenations. HBO preconditioning improved neurobehavioral scores and reduced mortality, decreased ischemic cell change, reduced the number of early apoptotic cells and hampered a conversion of early to late apoptotic alterations. HBO preconditioning reduced the immunoreactivity of phosphorylated p38 in vulnerable neurons and increased the expression of brain derived neurotrophic factor (BDNF) in early stage post-ischemia. However, preconditioning with 3 HBO treatments proved less beneficial than with 5 HBO treatments. We conclude that HBO preconditioning may be neuroprotective by reducing early apoptosis and inhibition of the conversion of early to late apoptosis, possibly through an increase in brain BDNF level and the suppression of p38 activation.



## STROKE LITERATURE

Neurosci Lett. 2007 Oct 2;425(3):141-5. Epub 2007 Aug 1.

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

**Beynon C, Sun L, Marti HH, Heiland S, Veltkamp R.**

Hyperbaric (HBO) and normobaric (NBO) oxygen therapy have been shown to be neuroprotective in focal cerebral ischemia. In previous comparative studies, NBO appeared to be less effective than HBO.

However, the experimental protocols did not account for important advantages of NBO in the clinical setting such as earlier initiation and prolonged administration. Therefore, we compared the effects of early prolonged NBO to delayed HBO on infarct size and functional outcome. We also examined whether combining NBO and HBO is of additional benefit. Wistar rats underwent filament-induced middle cerebral artery occlusion (MCAO) for 150 min. Animals breathed either air, 100% O<sub>2</sub> at ambient pressure (NBO; initiated 30 min after MCAO) 100% O<sub>2</sub> at 3 atm absolute (HBO; initiated 90 min after MCAO), or a sequence of NBO and HBO. Infarct volumes and neurological outcome (Garcia score) were examined 7d after MCAO. HBO (174±65 mm<sup>3</sup>) significantly reduced mean infarct volume by 31% compared to air (251±59 mm<sup>3</sup>) and by 23% compared to NBO treated animals (225±63 mm<sup>3</sup>). In contrast, NBO failed to decrease infarct volume significantly. Treatment with NBO+HBO (185±101 mm<sup>3</sup>) added no additional benefit to HBO alone. Neurological deficit was significantly smaller in HBO treated animals (Garcia score: 13.3±1.2) than in animals treated with air (12.1±1.4), but did not differ significantly from NBO (12.4±0.9) and NBO+HBO (12.8±1.1). **In conclusion, HBO is a more effective therapy than NBO in transient experimental ischemia even when accounting for delayed treatment-onset of HBO. The combination of NBO and HBO results in no additional benefit.**



## STROKE LITERATURE

Brain Res Rev. 2007 Jun;54(2):294-304. Epub 2007 Apr 27.

### **Effect of hyperbaric oxygenation on brain hemodynamics, hemoglobin oxygenation and mitochondrial NADH.**

**Meirovithz E, Sonn J, Mayevsky A.**

To determine the HbO(2) oxygenation level at the microcirculation, we used the hyperbaric chamber. The effects of hyperbaric oxygenation (HBO) were tested on vitality parameters in the brain at various pressures. Microcirculatory hemoglobin oxygen saturation (HbO(2)), cerebral blood flow (CBF) and mitochondrial NADH redox state were assessed in the brain of awake restrained rats using a fiber optic probe. The hypothesis was that HBO may lead to maximal level in microcirculatory HbO(2) due to the amount of the dissolved O(2) to provide the O(2) consumed by the brain, and therefore no O(2) will be dissociated from the HbO(2). Awake rats were exposed progressively to 15 min normobaric hyperoxia, 100% O(2) (NH) and to 90 min hyperbaric hyperoxia (HH) from 1.75 to 6.0 absolute atmospheres (ATA). NH and HH gradually decreased the blood volume measured by tissue reflectance and NADH but increased HbO(2) in relation to pO(2) in the chamber up to a nearly maximum effect at 2.5 ATA. Two possible approximations were found to describe the relationship between NADH and HbO(2): linear or logarithmic. These findings show that the increase in brain microcirculatory HbO(2) is due to an increase in O(2) supply by dissolved O(2), reaching a maximum at 2.5 ATA. NADH is oxidized (decreased signal) in parallel to the HbO(2) increase, showing maximal tissue oxygenation and cellular mitochondrial NADH oxidation at 2.5 ATA. In conclusion, in the normoxic brain, the level of microcirculatory HbO(2) is about 50% as compared to the maximal level recorded at 2.5 ATA and the minimal level measured during anoxia.

## STROKE LITERATURE

Neurosurg Focus. 2007 May 15;22(5):E13.

### **Preconditioning with hyperbaric oxygen attenuates brain edema after experimental intracerebral hemorrhage.**

**Qin Z, Song S, Xi G, Silbergleit R, Keep RF, Hoff JT, Hua Y.**

**OBJECT:** Preconditioning with hyperbaric oxygen (HBO2) reduces ischemic brain damage. Activation of p44/42 mitogen-activated protein kinases (p44/42 MAPK) has been associated with preconditioning-induced brain ischemic tolerance. This study investigated if preconditioning with HBO2 protects against intracerebral hemorrhage (ICH)-induced brain edema formation and examined the role of p44/42 MAPK in such protection. **METHODS:** The study had three experimental groups. In Group 1, Sprague-Dawley rats received two, three, or five consecutive sessions of preconditioning with HBO2 (3 ata, 100% oxygen, 1 hour daily). Twenty-four hours after preconditioning with HBO2, rats received an infusion of autologous blood into the caudate. They were killed 1 or 3 days later for brain edema measurement. Rats in Group 2 received either five sessions of preconditioning with HBO2 or control pretreatment and were killed 24 hours later for Western blot and immunohistochemical analyses. In Group 3, rats received an intracaudate injection of PD098059 (an inhibitor of p44/42 MAPK activation) before the first of five sessions of preconditioning with HBO2. Twenty-four hours after the final preconditioning with HBO2, rats received an intracaudate blood infusion. Brain water content was measured 24 hours after ICH. **RESULTS:** Fewer than five sessions of preconditioning with HBO2 did not significantly attenuate brain edema after ICH. Five sessions of preconditioning with HBO2 reduced perihematoma edema 24 and 72 hours after ICH ( $p < 0.05$ ). Strong p44/42 MAPK immunoreactivity was detected in the basal ganglia 24 hours after preconditioning with HBO2. Intracaudate infusion of PD098059 abolished HBO2 preconditioning-induced protection against ICH-induced brain edema formation. **CONCLUSIONS:** Preconditioning with HBO2 protects against brain edema formation following ICH. Activation of the p44/42 MAPK pathway contributes to that protection. Preconditioning with HBO2 may be a way of limiting brain injury during invasive neurosurgical procedures that cause bleeding.

Neurol Res. 2007 Mar;29(2):127-31.

### **Endothelial-neutrophil interactions during ischemia and reperfusion injury: basic mechanisms of hyperbaric oxygen.**

**Buras JA, Reenstra WR.**

Ischemia/reperfusion injury plays a central role in the development of tissue injury during multiple central nervous system diseases including acute stroke. Neutrophil adhesion to the endothelium indicates a major component of ischemia/reperfusion pathophysiology, and may be a target for therapeutic intervention. Hyperbaric oxygen has been documented to reduce ischemia/reperfusion injury in a number of different experimental models and in a single human randomized clinical trial. One mechanism responsible for the beneficial effect of hyperbaric oxygen in treatment of ischemia/reperfusion injury involves suppression of neutrophil-endothelial adhesion. This review intends to describe the current basic mechanisms responsible for hyperbaric oxygen-mediated inhibition of neutrophil-endothelial interactions following ischemia/reperfusion injury.

## STROKE LITERATURE

Int J Stroke. 2006 Nov;1(4):191-200.

### **Oxygen therapy in stroke: past, present, and future.**

**Singhal AB.**

Oxygen is frequently administered to patients with suspected stroke. However, the role of oxygen therapy in ischemic stroke remains controversial in light of the failure of three clinical trials of hyperbaric oxygen therapy to show efficacy, and the fear of exacerbating oxygen free radical injury. The previous trials had several shortcomings, perhaps because they were designed on basis of anecdotal case reports and little preclinical data. Most animal studies concerning oxygen therapy in stroke have been conducted over the last 6 years. Emerging data suggests that hyperbaric and even normobaric oxygen therapy can be effective if used appropriately, and raises the tantalizing possibility that hyperoxia can be used to extend the narrow therapeutic time window for stroke thrombolysis. This article reviews the history, rationale, mechanisms of action and adverse effects of hyperoxia, the key results of previous hyperoxia studies, and the potential role of oxygen therapy in contemporary stroke treatment.

Exp Neurol. 2006 Oct;201(2):316-23. Epub 2006 Jun 30.

### **Neuroprotective effect of hyperbaric oxygen therapy monitored by MR-imaging after embolic stroke in rats.**

**Henninger N, Küppers-Tiedt L, Sicard KM, Günther A, Schneider D, Schwab S.**

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  $145.3 \pm 39.6 \text{ mm}^3$  vs.  $202.5 \pm 58.3 \text{ mm}^3$  (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.



## STROKE LITERATURE

Brain Res Bull. 2006 Mar 31;69(2):109-16. Epub 2005 Dec 15.

**Involvement of the mitochondrial ATP-sensitive potassium channel in the neuroprotective effect of hyperbaric oxygenation after cerebral ischemia.**

**Lou M, Chen Y, Ding M, Eschenfelder CC, Deuschl G.**

In the present study, we investigated whether activation of mitochondrial ATP-sensitive potassium channel is involved in the neuroprotective effect offered by early hyperbaric oxygenation after cerebral ischemia. The selective mitochondrial ATP-sensitive potassium channel antagonist 5-hydroxydecanoate was infused intracerebroventricularly before hyperbaric oxygenation treatment initiated 3 h after middle cerebral artery occlusion for 90 min. Neurological status was evaluated and brains were removed for the measurement of infarct size and immunohistochemical evaluation of apoptosis 24 h after middle cerebral artery occlusion. **Early hyperbaric oxygenation treatment improved neurologic deficits and reduced infarct volume**, while these effects were reversed by the administration of 5-hydroxydecanoate. Furthermore, **early hyperbaric oxygenation significantly decreased the number of apoptotic cells in the peri-infarct cortex 24 h after ischemic insult** and this effect was also blocked by 5-hydroxydecanoate. The present findings suggest that early hyperbaric oxygenation therapy prevents apoptosis and promotes neurologic functional recovery after focal cerebral ischemia, and the opening of mitochondrial ATP-sensitive potassium channel plays a role in this antiapoptotic effect of early hyperbaric oxygenation.

## STROKE LITERATURE

Adv Ther. 2005 Nov-Dec;22(6):659-78.

**Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain trauma, and neurologic disease.**

**Al-Waili NS, Butler GJ, Beale J, Abdullah MS, Hamilton RW, Lee BY, Lucus P, Allen MW, Petrillo RL, Carrey Z, Finkelstein M.**

Hyperbaric oxygen (HBO) therapy has been used to treat patients with numerous disorders, including stroke. This treatment has been shown to decrease cerebral edema, normalize water content in the brain, decrease the severity of brain infarction, and maintain blood-brain barrier integrity. In addition, HBO therapy attenuates motor deficits, decreases the risks of sequelae, and prevents recurrent cerebral circulatory disorders, thereby leading to improved outcomes and survival. Hyperbaric oxygen also accelerates the regression of atherosclerotic lesions, promotes antioxidant defenses, and suppresses the proliferation of macrophages and foam cells in atherosclerotic lesions. Although no medical treatment is available for patients with cerebral palsy, in some studies, HBO therapy has improved the function of damaged cells, attenuated the effects of hypoxia on the neonatal brain, enhanced gross motor function and fine motor control, and alleviated spasticity. In the treatment of patients with migraine, HBO therapy has been shown to reduce intracranial pressure significantly and abort acute attacks of migraine, reduce migraine headache pain, and prevent cluster headache. In studies that investigated the effects of HBO therapy on the damaged brain, the treatment was found to inhibit neuronal death, arrest the progression of radiation-induced neurologic necrosis, improve blood flow in regions affected by chronic neurologic disease as well as aerobic metabolism in brain injury, and accelerate the resolution of clinical symptoms. Hyperbaric oxygen has also been reported to accelerate neurologic recovery after spinal cord injury by ameliorating mitochondrial dysfunction in the motor cortex and spinal cord, arresting the spread of hemorrhage, reversing hypoxia, and reducing edema. HBO has enhanced wound healing in patients with chronic osteomyelitis. The results of HBO therapy in the treatment of patients with stroke, atherosclerosis, cerebral palsy, intracranial pressure, headache, and brain and spinal cord injury are promising and warrant further investigation.

Cerebrovasc Dis. 2005;20(6):417-26. Epub 2005 Oct 17.

**Hyperbaric oxygen therapy of cerebral ischemia. - Helms AK, Whelan HT, Torbey MT.**

**BACKGROUND:** Hyperbaric oxygen (HBO) therapy of cerebral ischemia has been evaluated in a number of human and animal studies; however, there is presently no consensus on its efficacy. **METHODS:** We present a review of animal and human studies on HBO therapy of cerebral ischemia as well as present potential mechanisms of action of HBO. **RESULTS:** Animal studies of HBO have shown promise by reducing infarct size and improving neurologic outcome. HBO has also been shown to inhibit inflammation and apoptosis after cerebral ischemia. Early reports in humans also suggested benefit in stroke patients treated with HBO. Recent randomized, controlled human studies, however, have not shown benefit, although all were limited by small sample size. Important differences between animal and human studies suggest HBO might be more effective in stroke within the first few hours and at a pressure of 2-3 ATA. **CONCLUSIONS:** The clinical usefulness of HBO in the treatment of cerebral ischemia is not yet certain. Attention to emerging pathophysiologic data should be taken into consideration in design of any future clinical trials of HBO in acute ischemic stroke.



## STROKE LITERATURE

Undersea Hyperb Med. 2005 Sep-Oct;32(5):341-9.

### **Improvement in motor and cognitive impairment after hyperbaric oxygen therapy in a selected group of patients with cerebrovascular disease: a prospective single-blind controlled trial.**

**Vila JF, Balcarce PE, Abiusi GR, Dominguez RO, Pisarello JB.**

BACKGROUND: Clinical and experimental evidence suggests that a localized decrease in oxygen brain tissue availability contributes to the neurological deficit in patients with cerebrovascular disease (CVD) who also present with frontal leukoaraiosis (LA) (periventricular hypodensity on CT scan) and lacunar infarcts. In a prospective controlled trial blinded to patients but not to investigators, we tested the effect of HBO2 on this group of patients. METHODS: Selected patients with symptomatic CVD, LA and lacunar infarcts received daily exposures of 45 minutes for 10 days to hyperbaric oxygen (n=18, HBO2 group) or hyperbaric air (n=8, control group). The control group subsequently received HBO2. Scores of conventional scales for motor and cognitive functions were obtained and videotaped before and after exposure. After the exposures, participants were followed on a monthly basis with systematic clinical neurological examination for up to 6 months. Results. There was a statistically significant improvement in all scales for the HBO2 group compared with the placebo group and in the placebo group after receiving HBO2 (p<0.05). Neurological improvement persisted in the majority of patients for up to 6 months. Repetition of the HBO2 protocol in 9 patients in whom symptoms recurred after 6 months resulted in improvement of symptoms. CONCLUSIONS: These data provide evidence consistent with the notion that HBO2 improves neurological function in patients with CVD, lacunar infarcts and frontal LA. Because of the lack of investigator blinding and a relatively small sample size in this study, larger, randomized controlled studies are needed to further test this hypothesis and to further define the role of oxygen therapy for brain repair in chronic brain disease.

## STROKE LITERATURE

Stroke. 2005 Aug;36(8):1679-83. Epub 2005 Jul 14.

### **Hyperbaric oxygen reduces blood-brain barrier damage and edema after transient focal cerebral ischemia.**

**Veltkamp R, Siebing DA, Sun L, Heiland S, Bieber K, Marti HH, Nagel S,**

**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% O<sub>2</sub> 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 mm<sup>3</sup> (control) versus 47±10 mm<sup>3</sup> (HBO) at 15 minutes; 111±21 mm<sup>3</sup> versus 69±17 mm<sup>3</sup> 3 hours; 147±44 mm<sup>3</sup> versus 83±21 mm<sup>3</sup> 6 hours; 150±37 mm<sup>3</sup> versus 89±14 mm<sup>3</sup> 24 hours; and 322±52 mm<sup>3</sup> versus 215±21 mm<sup>3</sup> 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.

Pathophysiology. 2005 Jul;12(1):63-77.

### **Mechanisms of hyperbaric oxygen and neuroprotection in stroke.**

**Zhang JH, Lo T, Mychaskiw G, Colohan A**

Cerebral vascular diseases, such as neonatal encephalopathy and focal or global cerebral ischemia, all result in reduction of blood flow to the affected regions, and cause hypoxia-ischemia, disorder of energy metabolism, activation of pathogenic cascades, and eventual cell death. Due to a narrow therapeutic window for neuroprotection, few effective therapies are available, and prognosis for patients with these neurological injuries remains poor. Hyperbaric oxygen (HBO) has been used as a primary or adjunctive therapy over the last 50 years with controversial results, both in experimental and clinical studies. In addition, the mechanisms of HBO on neuroprotection remain elusive. Early applications of HBO within a therapeutic window of 3-6h or delayed but repeated administration of HBO can either salvage injured neuronal tissues or promote neurobehavioral functional recovery. This review explores the discrepancies between experimental and clinical observations of HBO, focusing on its therapeutic window in brain injuries, and discusses the potential mechanisms of HBO neuroprotection.



## STROKE LITERATURE

Crit Care Med. 2005 Apr;33(4):841-6.

**Effects of hyperbaric treatment in cerebral air embolism on intracranial pressure, brain oxygenation, and brain glucose metabolism in the pig.**

**van Hulst RA, Drenthen J, Haitsma JJ, Lameris TW, Visser GH, Klein J, Lachmann B.**

**OBJECTIVE:** To evaluate the effects of hyperbaric oxygen treatment after cerebral air embolism on intracranial pressure, brain oxygenation, brain glucose/lactate metabolism, and electroencephalograph.

**DESIGN:** Prospective animal study. **SETTING:** Hyperbaric chamber. **SUBJECTS:** Eleven Landrace/Yorkshire pigs. **INTERVENTIONS:** In 11 anesthetized pigs, intracranial pressure and brain oxygenation were measured with microsensor technology, brain glucose/lactate by microdialysis, and electroencephalograph by conventional methods. After injection of air into the internal carotid artery, animals were treated immediately (at 3 mins; t = 3) or at 60 mins (t = 60) with U.S. Navy Treatment Table 6 for 4.48 hrs. **RESULTS:** At the end of hyperbaric oxygen treatment, intracranial pressure in the t = 60 group (39 +/- 8 mm Hg) was significantly higher than in the t = 3 group (27 +/- 6 mm Hg), brain oxygenation values for group t = 3 and t = 60 were 66 +/- 14 and 52 +/- 15 mm Hg, respectively (no significant difference from baseline), and there were no pathologic scores in the visually assessed electroencephalograph. However, there was a significant decrease in brain glucose and a significant increase in brain lactate in both groups at the end of the 5-hr study period. **CONCLUSIONS:** Hyperbaric oxygen treatment initiated at both 3 and 60 mins after embolization decreased the deleterious effects of cerebral air embolism on intracranial pressure and brain metabolism. Therefore, this model appears suitable to test the application of hyperbaric oxygen treatment with a delay >60 mins after embolization, as is often the case in the clinical situation.