Hyperbaric oxygen in traumatic brain injury

Sarah B. Rockswold, Gaylan L. Rockswold and Archie Defillo

Division of Neurosurgery, Department of Surgery, Hennepin County Medical Center, Department of Neurosurgery, University of Minnesota, 701 Park Avenue, Minneapolis, MN 55415, USA

Objectives: *This critical literature review examines historical and current investigations on the efficacy and mechanisms of hyperbaric oxygen (HBO) treatment in traumatic brain injury (TBI). Potential safety risks and oxygen toxicity, as well as HBO's future potential, are also discussed.*
Methods: *Directed literature review.*
Results: *Historically, cerebral vasoconstriction and increased oxygen availability were seen as the primary mechanisms of HBO in TBI. HBO now appears to be improving cerebral aerobic metabolism at a cellular level, namely, by enhancing damaged mitochondrial recovery. HBO given at the ideal treatment paradigm, 1.5 ATA for 60 minutes, does not appear to produce oxygen toxicity and is relatively safe.*
Discussion: *The use of HBO in TBI remains controversial. Growing evidence, however, shows that HBO may be a potential treatment for patients with severe brain injury. Further investigations, including a multicenter prospective randomized clinical trial, will be required to definitively define the role of HBO in severe TBI.* [Neurol Res 2007; **29**: 162–172]

Keywords: Cerebral metabolism; hyperbaric oxygen; intracranial pressure; traumatic brain injury

Published by Maney Publishing (c) W. S. Maney & Son Limited

INTRODUCTION

Traumatic brain injury (TBI) is called the silent epidemic of the USA. Two million people suffer TBI each year in the USA and approximately one million of them require an emergency room visit; 500,000 are hospitalized and 50,000 die. This results in direct and indirect costs of 56 billion dollars annually to our country[1]. The magnitude of the problem is shown in the statement by Dr Thomas A. Ginnarelli, a neurosurgeon specializing in TBI: 'In the last twelve years, the number of deaths from head injury has exceeded all the military deaths in all the wars [up to the Vietnam War] fought by this nation since 1776'. Various drug and hypothermia multicenter trials have failed to show improvement in functional outcome and mortality rates in patients suffering from TBI[2–5]. In recent years, however, there has been promising animal and clinical research in the area of oxygen (O_2), especially hyperbaric oxygen (HBO), for the treatment of severe TBI[6–10].

The use of HBO in the treatment of TBI has been controversial. Oxygen toxicity and safety concerns have been at the forefront of this controversy. In truth, the complications from HBO have been rare and reversible in the authors' experience. Historically, HBO was seen as a mechanism to decrease cerebral blood flow (CBF) and intracranial pressure (ICP) while increasing O_2 availability to injured brain cells[11–13]. As highly technical equipment has become available in both TBI animal and clinical studies, however, HBO appears to be working at the mitochondrial level to improve cerebral aerobic metabolism after brain injury[7,8,10]. Clinically, HBO has been shown to decrease mortality rates and improve functional outcome in severely brain-injured patients[6,14,15]. As research on HBO continues, the goal is to accomplish a multicenter prospective randomized clinical outcome trial by which the efficacy of HBO in the treatment of severely brain-injured patients is evaluated.

Correspondence and reprint requests to: Gaylan L. Rockswold, MD, Division of Neurosurgery, Department of Surgery, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55415, USA. [gaylan.rockswold@co.hennepin.mn.us]

PATHOPHYSIOLOGY OF TBI

Ischemia has been implicated as a major cause of secondary brain injury and death following severe brain injury[16–18]. Inadequate O_2 supply to the traumatized brain results in the conversion of aerobic metabolism to anaerobic metabolism[19,20]. Anaerobic metabolism results in acidosis and depletion of cellular energy. As the demands for energy production are no longer met, the brain cells lose their ability to maintain ionic homeostasis. Abnormally high intracellular concentrations of calcium occur[21–23]. A combination of cellular acidosis and excessive concentrations of calcium activates various important intracellular proteins. This abnormal cellular environment results in the release of excitatory amino acids and in the formation of highly reactive free radicals that are extremely damaging to cell membranes[24–26]. The high levels of calcium also have been shown to lead to excessive calcium being absorbed on neuronal mitochondria membranes leading to the impairment of mitochondrial respiratory chain-linked oxidative phosphorylation leading to further functional failure of aerobic metabolism[27,28]. Mitochondrial dysfunction can persist for days following the initial insult[29–32].

Paradoxically, during this early phase of injury, metabolic needs of the injured brain tissue are increased

© 2007 W. S. Maney & Son Ltd
10.1179/016164107X181798

and CBF and delivery of O_2 in substrate are decreased. This results in what has been termed a 'flow/metabolism mismatch'[27]. Oxygen delivery to brain tissue is impaired not only by decreased CBF but by reduced O_2 diffusion into cells caused by vasogenic and cytotoxic edema. Studies have also shown that local brain tissue oxygen (PtO_2) levels are significantly correlated with ischemia and outcome[33–35]. Van den Brink *et al.* demonstrated the presence of early ischemia at the tissue level with reduced initial PtO_2 and found that low PtO_2 was an independent predictor of death and unfavorable outcome[34].

Many studies indicate that increased cerebrospinal fluid (CSF) lactate product is a marker for this anaerobic metabolism status caused either by a lack of O_2 (ischemia) and/or by damage to the mitochondria[18,19,33,36,37]. A continued high level of lactate in the brain has been shown to be a poor prognostic indicator after brain injury[19,37–39].

The time from the primary brain injury to the occurrence of irreversible cell damage resulting from ischemia and hypoxia varies considerably, depending upon the severity of the injury and the degree of hypoxia[40]. Brain tissue cannot survive without adequate delivery of O_2, and even short periods of O_2 deprivation may result in the activation of pathologic events that contribute to secondary cell damage. Supporting the aerobic processes of the threatened cells could possibly preserve viable, but non-functioning tissue.

HISTORICAL REVIEW OF HBO

The first paper published measuring the effect of HBO on CBF was written by Lambertson *et al.* in 1953[41]. Using the nitrous oxide method developed by Kety and Schmidt, they found a reduction of 24% in the CBF of conscious normal volunteers breathing O_2 at 3.5 atmospheres absolute (ATA) compared to 1 ATA[42]. However, their subjects hyperventilated at increased pressure, resulting in a fall of arterial PCO_2 by 5 mmHg. They concluded that the reduction in CBF was from the arterial hypocapnia.

There were no further published reports on HBO until the following decade. Early in the 1960s, there were two published articles by Illingworth *et al.* and Smith *et al.*, who found that there may be possible therapeutic value to HBO where it gave protection to an ischemic brain shown by electroencephalography[43,44]. However, there was debate whether this protection was negated by the cerebral vasoconstriction found by Lambertson *et al.*[41]. Jacobson *et al.* undertook an experiment measuring CBF and arterial and venous blood gasses with constant arterial PCO_2 in non-injured dogs[45]. They found a 21% reduction in CBF between dogs receiving 100% O_2 at 1 versus 2 ATA. The venous PO_2 remained relatively constant while there were large increases in the arterial PO_2 leading to an increased arterial–venous difference of oxygen ($AVDO_2$). They felt that this increase in the $AVDO_2$ showed that there was a homeostatic mechanism that exists to maintain tissue oxygen levels within fairly close limits and served to mitigate against the deleterious effects of HBO on the central nervous system. Also, because the arterial PCO_2 was held constant, they found that the decrease in CBF was a direct consequence of vasoconstriction. Tindall *et al.* also studied the effect of HBO on CBF in baboons[46]. He did not control arterial PCO_2 and found that there was a drop in CBF as well as arterial PCO_2 during the dive. Their conclusions were similar to that of Lambertson *et al.*[41].

During the mid-1960s, there were reports that the use of HBO may be beneficial in the treatment of cerebral ischemia[47–49]. However, there was one conflicting report by Jacobsen *et al.* that there were larger infarcts in the cerebrum following middle cerebral artery occlusion when HBO was used[50]. Of note was that the number of subjects described in all of these reports was very small.

The first study in which HBO was used to treat experimental TBI was carried out by Dunn *et al.*[51]. The authors exposed dog brains to liquid nitrogen simulating brain contusion. The animals were divided into six groups according to pressure and O_2 received. The mortality for all groups receiving hyperoxia was significantly decreased (15%) in comparison to those that did not (56%). The sizes of the lesions also were reduced in the HBO-treated group, although this finding did not reach statistical significance.

Sukoff *et al.* used two methods to produce cerebral edema in dogs, psyllium seeds and the extradural balloon technique[52]. Both series of dogs were divided into a HBO-treated group (3 ATA for 45 minutes) and a control group. Mortality in the psyllium seed group was 27% for the HBO-treated group and 83% for the control group. In the extradural balloon group, mortality was 50% for the HBO-treated group and 100% for the control group. All surviving HBO-treated dogs were neurologically normal. All animals were killed and their brains showed gross evidence of cerebral edema. However, the HBO-treated brains weighed significantly less than the control brains. They concluded that HBO has a protective effect against experimental cerebral edema.

Sukoff *et al.* published another paper on the effects of HBO on experimental edema[11]. This study was performed again in dogs, using the psyllium seed technique to produce a space occupying lesion. The animals were exposed at 3 ATA for 45 minutes at 8 hours intervals. The results were as follows: mortality rate for the control group was 83% compared to 27% in the HBO-treated group. Cisternal CSF pressure was steadily reduced in the HBO-treated group as compared to the control group which showed steady increase in ICP. They felt that the main action of HBO was at the level of the cerebral blood vessel. HBO caused cerebral vasoconstriction and decreased CBF reducing cerebral edema, yet at the same time, there was increased availability of O_2 at the cellular level. For these reasons, HBO could protect the injured brain against ischemia secondary to cerebral edema.

A similar study was performed by Moody *et al.*, using an extradural balloon in dogs[53]. The 95% mortality rate

Published by Maney Publishing (c) W. S. Maney & Son Limited

in the control group was reduced to 50% by treatment of the dogs with 100% O_2 at 2 ATA for 4 hours following balloon decompression. The quality of survival was good among the survivors of the HBO-treated group. They also concluded that HBO produces better tissue oxygenation during low CBF seen following this type of experimental brain injury.

The next important study on the effect of HBO on CBF was published by Wullenberg *et al.* from Dr Holbach's group in Germany[54]. This study was the first to measure CBF in severely brain-injured patients during HBO treatments. They used thermoprobes to measure the CBF. In contrast to previous published results, they found that CBF increased during the dive during increasing pressures, but once the pressure reached 2.5 ATA, no further rise occurred. During the same time period, blood pressure, pH and arterial PCO_2 remained normal. Arterial PO_2 increased to 1100 mmHg but venous PO_2 increased only slightly. The concentrations of lactate and pyruvate decreased corresponding to the rise in arterial PO_2. The CBF remained slightly elevated after the dive. They concluded that HBO is indicated in cases of severe brain injury.

Mogami *et al.* were one of the first to describe the effect of HBO on ICP in severely brain-injured patients[55]. Sixty-six patients in whom most (51) had TBIs were studied. The HBO treatment was usually given at a pressure of 2 ATA for 1 hour, two times a day; six of these treatments, however, were given at 3 ATA for 30 minutes. In total, 143 treatments were given to the 66 patients. During HBO, 33 patients (50%) showed clinical improvement during the treatment, but usually, regressions occurred after the treatments. CSF pressure was measured during treatment. The pressure was found to decrease during the beginning of treatment, stay at a low level during treatment and then rebound after treatment. The authors also found that lactate/pyruvate ratios were mildly decreased. This was the first published article that challenged that ICP decreases only from vasoconstriction. The group asserted that HBO may be affecting and stabilizing the blood–brain barrier. They also found that TBI has such heterogeneous pathophysiology that HBO may affect individuals differently.

Hayakawa *et al.* demonstrated clinical evidence that HBO treatment decreased CSF pressure[56]. There were two parts in this article, a clinical and experimental portion. The clinical study measured changes in CSF pressure in 13 patients with acute cerebral damage, nine who had TBI and four who underwent craniotomy for a brain tumor. PCO_2 was not controlled or measured. The authors described three main patterns during HBO treatment at 2 ATA for 1 hour: (1) in nine patients, CSF pressure decreased at the beginning of the dive, but rose again at the end; (2) in two patients, CSF pressure fell and remained lower after the dive; (3) in two patients, CSF pressure showed little change with the dive. In the experimental study, HBO was administered to 46 dogs at 3 ATA for 1 hour. Twelve of these dogs underwent extradural balloon technique to produce a brain injury. Both CBF and CSF pressure were measured. The response of the brain-injured dogs to the HBO was variable, but for most part, no or little change in CBF or CSF pressure was seen during and after HBO treatment. The authors concluded that there is considerable variation in the response of CSF pressure to HBO in patients and animals with brain injury, and like Mogami *et al.*, these differences needed to be studied and defined before HBO could be used in the treatment of TBI patients.

During the late 1960s and early 1970s, studies on HBO also were being carried out in Glasgow, Scotland. Miller *et al.* published several experimental animal studies which showed HBO could reduce CBF and ICP by direct cerebral vasoconstriction in injured dogs[57]. In one study, they showed that increased ICP was reduced by 23% by breathing 100% O_2 at normobaric pressures and 37% at 2 ATA in a HBO chamber[57]. The arterial blood pressure and arterial PCO_2 remained constant. They found that ICP was only responsive to HBO when autoregulation was still responsive to carbon dioxide. Another study showed that elevated ICP dropped during HBO treatment (26%), but not as much as with hyperventilation (34%)[13]. However, when HBO was used in conjunction with hyperventilation, an additional 25% drop in ICP was recorded. There was no significant change in CSF lactate in the HBO-treated group. Their conclusion was that HBO caused vasoconstriction, but at the same time, improved cerebral tissue oxygenation which protected the cells from damage.

The first article written by Holbach *et al.* studying the effect of HBO on glucose metabolism was published in 1972[58]. The main objective of this study was to determine the limits of O_2 tolerance in severely brain-injured patients to advance the use of HBO in the treatment of TBI. In this study, the effects of different HBO pressures (1–3 ATA) on cerebral glucose metabolism were studied in ten patients with severe TBI. The $AVDO_2$, arterial–venous differences of glucose (AVDG), lactate (AVDL) and pyruvate were taken. The glucose oxidation quotient (GOQ), which indicates cerebral glucose oxidative metabolism, was then calculated. At 1.5 ATA, a well-balanced cerebral glucose metabolism was maintained, indicated by a normal GOQ of 1.35. There was also a decrease in lactate and lactate/pyruvate ratio. However, Holbach *et al.* found that exposure of HBO at 2 ATA led to a decrease in oxidative glucose metabolism shown by a significantly reduced uptake of O_2 in comparison to glucose as well as a rise in lactate and lactate/pyruvate levels[58]. They found that the increased pressure interfered with oxidative energy formation and led to a compensatory increase of anaerobic energy production and hyperglycolysis.

By 1973, Holbach wrote: 'The real indication for the hyperbaric oxygen therapy is the deficiency of oxygen in the brain tissue because brain hypoxia is an essential factor of…secondary hypoxic brain lesions'[59]. He reviewed his past work, stating that HBO caused a marked rise in arterial O_2 pressure (8–10-fold increment at 1.5 ATA and 12-fold increment at 2 ATA), while the arterial O_2 pressure in the jugular bulb venous flow rose only slightly resulting in a marked increase in cerebral

Published by Maney Publishing (c) W. S. Maney & Son Limited

$AVDO_2$. He also reiterated the findings of the 1972 study which showed that 1.5 ATA was the ideal pressure based on oxidative glucose metabolism. Finally, the results of a randomized trial between patients treated with 1.5 versus 2.0 ATA were described. Two hundred and sixty-seven HBO treatments were given to 102 patients: 50 patients treated with 1.5 ATA and 52 treated with 2.0 ATA. Forty-eight percent of the patients treated with 1.5 ATA had a good outcome versus 25% of the patients treated with 2.0 ATA. This improvement in functional outcome was statistically significant.

An important clinical study was published by Holbach *et al.* in 1974[14]. This paper strongly suggested that HBO applied systematically may improve the outcome of patients who were severely brain-injured. The study included 99 patients with traumatic midbrain syndrome, every other one of whom was treated with HBO at 1.5 ATA for 30 minutes. Each patient received between one and seven treatments which was determined on each patient's response to the HBO. The overall mortality rate for the 49 HBO-treated patients was 33% as compared to the control patients which was 74%. Functional outcome also was improved with 33% of the HBO-treated patients having a good outcome compared to 6% of the control patients. Patients with cerebral contusions less than 30 years of age were particularly benefited by HBO. They found that the increased survival and functional outcome in the HBO-treated group was secondary to decreased ICP as well as improved oxidative glucose metabolism.

The final publication by Holbach *et al.* was in 1977 (Ref. 60). This study measured the effect of HBO at 1.5 and 2 ATA on cerebral glucose metabolism in 23 TBI patients and seven anoxic brain-injured patients. Many of their previous findings on the effect of pressure on glucose metabolism were replicated in this study. They found that the injured brain would not tolerate HBO exposure at 2 ATA for 10–15 minutes, but exposure at 1.5 ATA for 35–40 minutes was well tolerated and glucose metabolism was improved. An important finding for future work was that the $AVDO_2$ values remained unchanged after the 1.5 ATA HBO treatments from baseline measurements.

Another clinical study was published by Artru *et al.*, evaluating the effectiveness of HBO in the treatment of severely brain-injured patients[15]. The study was a prospective trial of 60 patients randomized into an HBO treatment group and a control group. The HBO was administered at 2.5 ATA for 60 minutes. The treatment sequence was ten daily sessions, no session for 4 days, followed by ten more daily sessions until the patient either recovered consciousness or died. There was a time delay between injury and onset of HBO treatment averaging 4.5 days. Only 17 of the 31 patients received four daily treatments in the first week secondary to treatment interruptions. No difference in mortality at year 1 was seen between the two groups; however, infectious complications were the primary reason for death in both groups. Functional outcome was improved at month 1, in younger patients treated with HBO, who had a clinical picture of brainstem contusion. The authors found that the delay in treatment and frequent interruptions of treatment may have led to the study's poor results.

A second paper written by Artru *et al.*, also published in 1976, studied the effect of HBO on cerebral metabolism in severely brain-injured patients[61]. Six patients were treated with HBO at 2.5 ATA, timing between dives is not known. CBF, $AVDO_2$, AVDG and AVDL as well as CSF parameters were measured 2 hours pre-dive and 2 hours post-dive. The cerebral metabolic rates of oxygen ($CMRO_2$), glucose (CMRG) and lactate (CMRL) were calculated from those measurements. Pre-dive arterial and CSF lactate levels were found to be high while pre-dive CBF and $CMRO_2$ were lower than normal. They found that the $AVDO_2$ remained constant before and after the dives as had Holbach *et al.*[60]. The CBF was raised in patients who had low CBF values before the dive and was reduced in the patients who started with a high CBF. Each patient's $CMRO_2$ values followed the direction of their CBF. The effects of the HBO treatment did not last until the next pre-dive measurement and the patients reacted to each HBO treatment consistently. The spinal CSF lactate, CMRL and CMRG did not significantly change. The authors concluded that HBO can improve CBF when there is cerebral edema or intracranial hypertension.

In 1982 Sukoff *et al.* published an article studying the effect of HBO on CBF and ICP in TBI[12]. Their theory was that HBO reduced ICP by decreasing CBF but concomitantly increased cerebral oxygenation leading to a decrease in cerebral ischemia. Entered into the study within 6 hours of injury, 50 comatose TBI patients were treated with HBO at 2 ATA for 45 minutes every 8 hours for 2–4 days. The ICP was decreased in all patients in whom measurements were obtained. This reduction ranged between 4 and 21 mmHg below the pre-dive level and was sustained for 2–4 hours after HBO treatment was completed. Sukoff *et al.* recorded only the lowest ICP value during the HBO treatment and did not report all ICP measurements recorded throughout the dive[12]. There were no reports of pulmonary toxicity. They found that additional studies on the effect of HBO on ICP and cerebral metabolism were needed.

The above investigations of HBO had several weaknesses. Most of the protocols were not uniform and the number of subjects was small. Although Holbach *et al.* had shown that the ideal depth was 1.5 ATA for treatment of TBI, HBO was delivered at 2–3 ATA in most of the experimental and clinical studies[14,58–60]. In the clinical trials, the severity of brain injury is not known as Glasgow coma scale (GCS) scoring was not used. In addition, none of the trials were truly randomized. Despite these shortcomings, positive results on the efficacy of HBO in TBI were consistently found.

The first paper to show that HBO had a persistent effect on cerebral glucose metabolism following treatment was published by Contreras *et al.*[62]. The authors measured glucose utilization with the autoradiographic 2-deoxyglucose technique in rats injured by a focal

Published by Maney Publishing (c) W. S. Maney & Son Limited

parietal cortical freeze lesion. This cold lesion was felt to correspond with a focal brain contusion. Four groups of rats were used: (1) sham-lesioned group, no treatment; (2) sham-lesioned, HBO treatment; (3) cold-lesioned, no treatment; (4) cold-lesioned, HBO treatment. The HBO treatments at 2 ATA for 90 minutes were carried out daily for 4 consecutive days. Initially, glucose utilization was decreased throughout the brain, especially ipsilateral to the lesion. Glucose utilization, however, tended to be increased 5 days after injury in the HBO-treated cold-lesioned rats as compared to the control cold-lesioned group. This improvement reached statistical significance in five of the 21 structures examined, which were the auditory cortex, the medial geniculate body, the superior olivary nucleus, the lateral geniculate body ipsilateral to the lesion and the mamillary body. An interesting finding was that HBO decreased glucose utilization in sham-lesioned rats. Their results indicate that HBO improves glucose utilization in a cold-lesion rat model, especially in the gray matter structures close to the actual lesion. Their novel finding was that the increase persisted for at least 1 day after termination of HBO exposure. They were unsure of the mechanism involved with this persistence, but felt that further studies were indicated.

A paper which studied the effects of HBO on the blood–brain barrier was published by Mink *et al.*[63]. Rabbits were subjected to cerebral ischemia by CSF compression. They were allowed to reperfuse for 30 minutes and then either treated with HBO at 2.8 ATA for 125 minutes followed by 90 minutes of 100% FiO_2 or with 100% O_2 for 215 minutes. CBF and vascular permeability were measured at the end of the reperfusion period and 90 minutes after termination of the treatments. HBO treatment statistically lowered CBF in the HBO-treated group as compared with the controls. Vascular permeability also was statistically lowered by 16% in the gray matter and 20% in the white matter. Somatosensory evoked potentials (SEP) were similar between both groups. The authors concluded that HBO was promoting the blood–brain barrier integrity following global cerebral ischemia in a rabbit model. CBF also was reduced and this effect was not associated with a reduction in the SEP recovery. The results suggested that if there were any detrimental effects of free radical generation with HBO treatment, they were outweighed by the beneficial effects of HBO.

An important paper investigating the mechanisms by which HBO improved ischemic tissue O_2 capacitance was published by Siddiqui *et al.*[64]. The authors measured subcutaneous tissue O_2 treatment in an ischemic rabbit ear model before, during and after HBO treatment followed by 100% O_2 versus those treated only with 100% O_2. The HBO treatment, which was at 2 ATA for 90 minutes, was performed daily for 14 treatments. The tissue responsiveness, measured by O_2 tissue tension, was found to increase on successive days from an ischemic baseline to well above a non-ischemic level. The authors found that there was 'a consistent and striking response to 100% oxygen (at 1 ATA) by ischemic tissue undergoing serial hyperbaric oxygen therapy'. This responsiveness was not found in tissue that was treated only with 100% O_2 at 1 ATA. The group asserted that this tissue responsiveness indicates the tissue's ability to accept and potentially use O_2 and that HBO was responsible for this change. They found that cells in the ischemic region may see the supraphysiologic elevation of tissue O_2 partial pressure as a trigger that signals that enough O_2 is in the environment to proceed with normal healing. Subsequent exposure to 100% O_2 reinforces this signal and also supplies the O_2 needed to continue the repair. They concluded that 'molecular oxygen, when delivered at high pressure, can function both as a respiratory metabolite and as a signal transducer'.

Rockswold *et al.* published the first modern prospective randomized clinical trial on the efficacy of HBO in the treatment of severely brain-injured patients[6]. All patients who were entered had suffered closed head injury with a GCS score of 9 or less. The patients were entered into the study between 6 and 24 hours post-injury. One hundred and sixty-eight severely brain-injured patients were randomized into two groups: the first group receiving HBO treatments and the second serving as a control group. Eighty-four patients received HBO with 100% O_2 at 1.5 ATA for 60 minutes. Treatments were given every 8 hours for 14 days unless the patient began following commands or became brain dead. Treatments were discontinued if the patient required a fraction of inspired oxygen (FiO_2) of 50% or greater to maintain an arterial PO_2 greater than 70 mmHg. The GOS was used as the primary tool for assessing outcome. Of the 168 patients, only two control patients were lost to follow-up at month 12.

The mortality rate for the 84 HBO-treated patients was 17% and for the 82 control patients was 32% ($p<0.05$). This improvement suggests a 50% relative reduction in mortality. In addition, mortality rate was improved in specific subgroups. In the 47 patients with ICP values persistently greater than 20 mmHg, the mortality rate was 21% as opposed to 48% mortality in the 40 patients with elevated ICP who served as controls ($p<0.02$). Functional recovery was evaluated 12 months post-injury using the GOS. Favorable outcome was defined as good recovery or moderate disability. Overall, there was no significant improvement in favorable outcome in the 84 patients treated with HBO in comparison to the 82 control patients. However, some specific subgroups did show improved favorable outcome. The 33 patients with surgically evacuated mass lesions had a 45% favorable outcome at year 1 as opposed to a 34% favorable outcome in the 41 patients with surgically evacuated mass lesions who served as control. This indicates a 33% relative improvement. It is now thought that with an appropriately increased '*n*', this difference would be statistically significant. Mean peak ICP was significantly reduced in HBO-treated patients as opposed to controls.

Of major importance is the fact that the 84 patients in the treatment group received a total of 1688 HBO treatments for an average of 21 treatments. Considering the number of treatments delivered, relatively few

Published by Maney Publishing (c) W. S. Maney & Son Limited

complications occurred. They were all pulmonary in nature, manifested by an increased FiO_2 requirement and frequently, chest X-ray infiltrates. In ten patients, the HBO treatments were stopped. All pulmonary changes were reversible. There were no permanent sequelae that occurred from the 1688 HBO treatments that were delivered.

This clinical outcome study showed that HBO can be administered to severely brain-injured patients safely and systematically and that mortality rates for severely brain-injured patients are reduced by ~50% with HBO treatments, particularly in patients with GCS scores of 4–6, those with mass lesions and those with increased ICP. These three factors are interrelated and without HBO treatment, the mortality rate would be the highest in these groups of patients because all are indicative of poor prognosis. Thus, through reducing ICP and probably improving aerobic glucose metabolism, HBO allowed these severely brain-injured patients to survive. The authors were unsure why the functional recovery overall was not improved with this treatment paradigm but hypothesized that too much O_2 was given to patients with less severe injuries, i.e. higher GCS score, contusion or normal ICP. They found that the protocol should be more individualized.

Many questions persisted about the efficacy and application of HBO in TBI following the above prospective randomized clinical study. Further investigation was needed to elucidate the potential metabolic effects of HBO on severely brain-injured patients. A prospective, clinical physiologic study, therefore, was undertaken to determine the effects of HBO on CBF, cerebral metabolism and ICP[7].

Thirty-seven patients treated for severe TBI were entered into the study within 24 hours of admission. All patients had a GCS score 8 or less and CT scan scores were ⩾II in conformance with the classification system of the Traumatic Coma Data Bank. The patients received HBO with 100% O_2 at 1.5 ATA for 60 minutes. The mean time from injury to initial HBO treatment was 23 hours. Treatment was administered on subsequent days for a total of five treatments. CBF using the nitrous oxide method, $AVDO_2$, $CMRO_2$, ventricular CSF lactate levels and ICP values were obtained 1 hour before HBO and 1 and 6 hours post-HBO. The patients were then assigned to reduced, normal or raised categories according to the CBF classification system developed by Obrist *et al.* and modified by Robertson *et al.*[65,66].

In patients in whom CBF levels were reduced before HBO, both CBF and $CMRO_2$ were raised 1 and 6 hours after HBO ($p=0.001$). In patients in whom CBF levels were normal before HBO, both CBF and $CMRO_2$ levels were increased at hour 1 ($p<0.05$), but not at hour 6. CBF was reduced 1 and 6 hours after HBO ($p=0.007$), but $CMRO_2$ was unchanged in patients who exhibited raised CBF before HBO.

Levels of CSF lactate were consistently decreased 1 and 6 hours after HBO, regardless of the patients' CBF category before undergoing HBO ($p=0.011$). Pre-dive CSF lactate levels for individual HBO treatments were inversely related to the pre-dive CBF values demonstrating that in those HBO sessions in which patients began with a reduced CBF value, CSF lactate pre-treatment levels were significantly greater than those seen in HBO in which patients began with normal or raised CBF ($p=0.003$). This finding may indicate that patients with reduced pre-dive CBF were the most ischemic or had the most severe cellular dysfunction in the brain and responded to HBO treatment most dramatically.

ICP was measured before, during the HBO treatment and until the next HBO treatment. The ICP values rose throughout the dive except for a trend for patients with elevated ICP (⩾15 mmHg) to improve during the pressurization phase and the first 15 minutes of the HBO treatment. Patients with elevated ICP also showed a consistent and highly significant decrease in their ICP from the time of the completion of the HBO treatment to 6 hours post-treatment ($p=0.006$).

The results of this study indicate that HBO may have improved the ability of ischemic or damaged brain tissue to use the O_2 received in baseline FiO_2 for at least 6 hours following the HBO. This led to improved $CMRO_2$ and decreased CSF lactate levels, which also persisted for at least 6 hours, indicating a shift toward aerobic metabolism. The authors hypothesized that CBF rises in response to this increased cerebral metabolism. When CBF and $CMRO_2$ are normally metabolically coupled, the ratio between them does not change; in other words, the $AVDO_2$ remains constant. This trend for HBO to normalize metabolic coupling of CBF and cerebral metabolism was the most apparent in patients with reduced CBF or with ischemia as documented by high lactate levels.

The authors found that the potentially noxious stimuli of heat and pressure in the paranasal sinuses may have overridden any benefit that HBO had on the patient's ICP during treatment. However, in patients who began their dive with a high ICP, HBO reduced their ICP (⩾15 mmHg) for at least 6 hours following treatment. In this study, HBO also lowered CBF in patients who began their treatment with a raised CBF and did so without significantly reducing their $CMRO_2$. Raised CBF or hyperemia has been shown to be related to increased ICP, brain edema and poor outcome. The authors felt that HBO may promote blood–brain barrier integrity, reducing cerebral edema and hyperemia, which in turn helped to lower elevated ICP.

In 2004, an important basic science article was published by Daugherty *et al.* studying the mechanism of action that HBO has on TBI[9]. The authors produced strong supporting experimental data for clinical observations of Rockswold *et al.*[7]. Four groups of rats were compared: (1) sham-injured, 30% FiO_2 for 4 hours; (2) sham-injured, 1 hour HBO (1.5 ATA) followed by 3 hours of 100% FiO_2 at 1 ATA; (3) fluid percussion injured, 30% FiO_2 for 4 hours; (4) fluid percussion injured, 1 hour HBO (1.5 ATA) followed by 3 hour 100% FiO_2 at 1 ATA. Fluid percussion injury was delivered at 2.1 ± 0.05 ATA to the rats[67,68]. PtO_2 levels were measured by a Licox probe into the cortex near the cortical hippocampal junction. This placement allowed

Published by Maney Publishing (c) W. S. Maney & Son Limited

for the measurement of brain PtO_2 under the injury site. *Ex vivo* measurements of global brain tissue oxygen consumption (VO_2) were made using the Cartesian diver microrespirometer methodology described by Levasseur *et al.*[69]. *Ex vivo* measurements of mitochondrial metabolic activity (redox potential) were carried out in a synaptosomal preparation to enrich for mitochondria. Mitochondrial redox potential was measured using an Alamar blue fluorescence technique[70,71].

Brain PtO_2 was significantly improved in both the injured and sham-injured animals that received HBO treatment as compared to the ones receiving only 30% O_2. Injured animals tended to have a lower brain PtO_2 levels as baseline compared to the sham-injured ones. Baseline brain PtO_2 levels were 37.7 mmHg in injured animals receiving 30% O_2. This value went to ~103 mmHg on 100% O_2 at 1.0 ATA and finally to 247 mmHg on HBO at 1.5 ATA. The dramatic relative 250% increase in brain PtO_2 levels, when going from 100% O_2 at 1 ATA to 100% O_2 at 1.5 ATA, was not clear. Under normobaric conditions, the amount of dissolved O_2 in the blood is relatively small (0.3 ml/dl in air at atmospheric pressure). HBO at 1.5 ATA increases the amount of dissolved O_2 by ten-fold (3.2 ml/dl), therefore increasing the arterial PO_2. One hypothesis for explaining the relatively high brain PtO_2 in relationship to arterial PO_2 is that this dissolved O_2 in plasma is more readily available to brain tissue than hemoglobin-bound O_2.

The combined HBO/100% FiO_2 treatment paradigm described also caused a highly significant increase in global VO_2 in both injured and sham-injured animals when compared to control animals receiving 30% O_2. Brain tissue VO_2 is a marker for cerebral aerobic metabolism and corresponds to $CMRO_2$ values used clinically in patients. CBF and VO_2 are closely coupled and respond to cellular activity. Daugherty *et al.* felt that the findings of increased VO_2 after HBO treatment strongly support that HBO improves aerobic metabolism in the injured brain[9].

Mitochondrial redox potential was significantly reduced by the fluid percussion injury when compared to sham-injured animals in both the HBO and 30% FiO_2 groups at the completion of 1 hour of treatment. However, following the 1 hour HBO treatment plus 3 hours of 100% O_2 at 1 ATA, mitochondrial redox potential was reversed to near sham-injured animal levels. When the authors compared the effects of the different treatments at hour 4, the injured animals that had received the HBO treatment had significantly increased mitochondrial redox potential in all areas of the brain sampled when compared to the injured animals that had received 30% O_2. These data indicate that mitochondrial function may be depressed after TBI, but there is a potential for mitochondrial functional recovery and that HBO can enhance this recovery.

Recent experimental evidence in the same lateral fluid percussion TBI rat model has demonstrated improved cognitive recovery, increased cerebral ATP levels and reduced hippocampal neuronal cell loss with HBO followed by normobaric hyperoxia[10]. For the cognitive recovery portion of the study, 205 rats were divided into four groups 15 minutes after injury: (1) sham-injured; (2) fluid percussion injured, 30% FiO_2; (3) fluid percussion injured, 100% O_2 in the HBO chamber at 1.5 ATA for 1 hour and at 1 ATA for additional 3 hours; (4) fluid percussion injured, 100% O_2 in the HBO chamber at 1 ATA for 4 hours. On days 11–15 following injury, cognitive function was assessed by the Morris Water Maze test. The results demonstrated that when compared to sham animals, all three injured groups described above had longer goal latencies. However, the combined HBO/FiO_2-treated group showed significantly shorter goal latency than the other two groups for all time points. By day 15, the cognitive deficit was markedly attenuated in the HBO/100% O_2-treated group, but not in the 100% O_2-treated group or control animals.

For ATP measurement, the rats in each group were given only 1 hour of treatment, whether it was 30% O_2, HBO or normobaric hyperoxia. The combination of HBO and 100% O_2 was not studied. ATP was extracted from the cerebral cortex and measured using high performance liquid chromatography system. Immediately following injury, ATP levels were significantly decreased in all injured animals when compared to sham-injured animals. However, after 1 hour of treatment, both groups of animals that received hyperoxia had significantly elevated ATP levels when compared with the injured animals that received 30% O_2. In fact, the ATP levels were close to the levels of the sham-injured group.

Twenty-one days post-injury, four rats in each group were killed to assess hippocampal neuronal loss. Cranial sections throughout the hippocampus were examined with an Olympus Image System Cast Program. The HBO/100% FiO_2 combined group had significantly reduced injury-induced cell loss in the CA2–3 region of the hippocampus when compared to control or animals receiving normobaric hyperoxia alone. No significant differences in peroxide, peroxynitrite or free radical production between the sham-injured animals and the injured animals treated with 30% O_2, 100% O_2 or HBO 1 or 4 hours post-treatment were found. The results of this study strongly corroborate the findings that HBO used in combination with normobaric hyperoxia enhances cellular metabolism and supports the concept that this enhancement provides a protective effect for severe TBI.

POTENTIAL MECHANISM OF HBO

Historically, the mechanism through which HBO worked was found to be vasoconstriction of the cerebral blood vessels which led to decreased CBF and ICP. The vasoconstriction was not found to be deleterious because O_2 availability to the injured cells was greatly increased[11,13]. As experimental research continued and more evidence accumulated, however, HBO appeared to be decreasing cerebral edema and stabilizing the blood–brain barrier as well[52,55,63]. Recent clinical studies on the effect of HBO corroborate these findings

Published by Maney Publishing (c) W. S. Maney & Son Limited

with elevated ICP being improved persistently after treatment[6,7,12].

HBO appears to improve aerobic metabolism in severely brain-injured patients. Following severe TBI, there is a relative energy crisis with depression of cerebral mitochondrial function. Impaired mitochondrial respiration results in a shift from aerobic to anaerobic metabolism with resultant increased lactate and reduced ATP production[29,30]. At the same time, delivery of O_2 to the brain tissue is reduced by both decreased local CBF as well as diminished O_2 diffusion secondary to cerebral edema. HBO allows the delivery of supranormal amounts of O_2 to the injured brain cells through increasing dissolved O_2 in the blood and improved CBF[7,9]. In addition, work by several investigators suggests that HBO allows the injured brain to use baseline amounts of O_2 more efficiently following treatments and has a persistent effect on the injured brain tissue[7,9,60–62]. There is a growing amount of experimental animal evidence that this change occurs at the mitochondrial level[9,10]. The exact mechanism by which HBO may enhance mitochondrial recovery is unknown.

SAFETY AND OXYGEN TOXICITY ISSUES

Most neurosurgeons treating severe TBI are only familiar with HBO treatment in a relatively vague way. Even among neurosurgeons more familiar with the technique, the idea of placing an intubated, severely brain-injured patient with multiple injuries into an HBO chamber, particularly a monoplace, seems prohibitive[72]. One of the challenges in establishing HBO as an accepted therapy for severe TBI is to establish its safety as well as the efficacy of the treatment.

Fortunately, for both the TBI patient and the treating physician, the landmark investigations of Holbach *et al.* established the ideal HBO treatment pressure at 1.5 ATA[58–60]. This is a relatively 'shallow dive' as far as HBO treatment protocols are concerned, which are typically in the 2.0–3.0 ATA level. The intermittent 60 minute HBO treatment administered every 6–8 hours at 1.5 ATA greatly reduces potential safety and toxicity issues.

Based on our own past and continuing investigations, as well as that of Weaver *et al.* placing severe TBI patients in either a monoplace or multiplace HBO chamber at 1.5 ATA for 60 minutes is a very low risk procedure[6,7,73–76]. Monoplace chambers are much less expensive than multiplace chambers and can be placed in or near the intensive care unit. In fact, the monoplace chamber becomes an extension of the critical care environment. Continuous monitoring of ICP, mean arterial pressure (MAP), cerebral perfusion pressure (CPP), end tidal CO_2 and brain tissue oxygen can be performed. In addition, central venous pressure or Swan-Ganz catheter monitoring are carried out if needed. Careful evaluation of the patient's pulmonary status before HBO treatment is critical. In our work, we have regarded a baseline FiO_2 requirement of greater than 50% and a positive end expiration pressure of greater than 10 to maintain adequate oxygenation as contraindications to HBO. It is essential to maintain adequate ventilation throughout the treatment. In the case of an emergency, an intubated ventilated patient can be decompressed and out of the chamber in 2 minutes. We routinely perform myringotomy to reduce patient stimulation during treatment and thereby, ICP[6].

The lung is the organ most commonly damaged by hyperoxia because the O_2 tension in the lungs is substantially higher than in other tissues[77]. The mechanism by which pulmonary injury occurs has been termed 'oxidative stress'[78,79]. Central to this process is the release of proinflammatory cytokines by alveolar macrophages, specifically IL-8 and IL-6, and the subsequent influx of activated cells into the alveolar air space[80,81]. Measurement of these proinflammatory cytokines in bronchial alveolar lavage has been shown to be predictive of acute lung injury and pulmonary infection in exposure to super physiologic concentrations of inspired O_2[82].

The concept of 'unit pulmonary toxic dose' (UPTD) has been developed and allows comparison of the pulmonary effects of various treatment schedules of hyperoxia[83,84]. One UPTD is equal to 1 minute of 100% O_2 at 1 ATA. Appropriate conversion factors (Kp), that is, multipliers of 1 minute of 100% O_2 at 1 ATA, allow one to quantitate the pressure (ATA) of the O_2 exposure. In general, it is recommended that total O_2 exposure in a single treatment be limited to a UPTD of 615 or less. The extreme limit of a single O_2 exposure is 1425 UPTD. This dose will produce a predicted 10% decrease in vital capacity in a normal individual. A 1 hour HBO treatment at 1.5 ATA is equal to 60×1.78 Kp or 106.8 UPTD. In our first study, 1 hour treatments at 1.5 ATA were delivered every 8 hours producing 320 UPTD per day[6]. The 24 hours of 100% O_2 at 1 ATA, which was described in the recent article by Tolias *et al.*, is the equivalent of 1440 UPTD[8]. This number exceeds the extreme upper limit for a single O_2 exposure. Therefore, relatively speaking, a 1 hour HBO treatment of 1.5 ATA delivers a low dose of O_2. In the clinical trial described previously in which 84 TBI patients received 1688 HBO treatments, no permanent sequelae resulted[6]. Pulmonary complications occasionally occurred (ten of 84 patients), but all were reversible.

Oxygen, especially under increased pressure, also may cause potential cerebral toxicity. Brain tissue is especially vulnerable to lipid peroxidation because of its high rate of O_2 consumption and high content of phospholipids. Additionally, the brain has limited natural protection against free radicals, i.e. it has limited scavenging ability, poor catalase activity and is rich in iron, which is an initiator of radical generation in brain injury[25,85–87]. There are experimental studies demonstrating increased formation of reactive O_2 radicals and secondary lipid peroxidation in the brain, but the depth and duration of HBO treatment in theses studies are much greater than used in our clinical investigations[88–90]. There is no clinical evidence for cerebral toxicity using an HBO treatment paradigm of 1.5 ATA

Published by Maney Publishing (c) W. S. Maney & Son Limited

for 60 minutes. However, to further evaluate this issue, we are monitoring ventricular CSF F2-isoprostane which is isometric to cyclo-oxygenase and is derived from prostaglandin F2[91,92]. CSF F2-isoprostane is exclusively produced from free radical catalyzed peroxidation of arachidonic acid. It is a specific quantitative biomarker of lipid peroxidation *in vivo* in the brain. F2-isoprostane values have not been elevated in our current study (unpublished data).

In conclusion, HBO treatments at a depth of 1.5 ATA can be delivered to the severe TBI patient with or without multiple injuries in either a monoplace or multiplace chamber with relative safety and low risk of O_2 toxicity.

PRESENT AND FUTURE DIRECTIONS

The authors are currently carrying out a prospective, randomized clinical trial for severe TBI patients designed as three-treatment comparison, i.e. HBO, normobaric hyperoxia and control, funded by the National Institute of Neurological Disease and Stroke. HBO is delivered for 60 minutes at 1.5 ATA and normobaric hyperoxia (100% FiO_2) for 3 hours. The treatments are given every 24 hours for 3 days. Recent studies have described normobaric hyperoxia (100% FiO_2) as a method of delivering supernormal levels of O_2 to severe TBI patients[8,27]. Improvement in cerebral metabolism and reduced ICP have been described. The relative ease of administration and its inexpense require that normobaric hyperoxia be evaluated as an alternative treatment to HBO.

This is not a clinical outcome study. However, surrogate outcome variables which predict and correlate with clinical outcome will be studied. They are measured before initiation of therapy, during administration of therapy, and for 24 hours following therapy. Continuously monitored outcome variables include ICP, PtO_2, microdialysate lactate, glucose, pyruvate and glycerol. CBF, $AVDO_2$, $CMRO_2$, CSF lactate, F2-isoprostanes and bronchial lavage fluid (IL-8 and IL-6 assays) are being obtained once before treatment, during treatment, and 1 and 6 hours post-treatment. The results of the trial will allow a direct comparison of HBO and normobaric hyperoxia in terms of their treatment efficacy on the surrogate outcome variables as well as their relative toxicity. In addition, post-treatment effects will be compared statistically to pre-treatment values. The duration of the effect will be determined. Traumatic brain injury is very heterogeneous in terms of lesions and severity. The study will allow us to determine which severe TBI patients respond to therapy in terms of their GCS scores and lesion types.

The work described above by Daugherty and Zhou from the laboratory at the Medical College of Virginia, has prompted a fourth treatment arm in this study[9,10]. That is a combination of HBO for 60 minutes at 1.5 ATA followed by 3 hours of 100% FiO_2 at 1.0 ATA. The hypothesis to be tested is that improvement in cerebral metabolism does not occur during the HBO treatment, but HBO treatment results in improved use of O_2 by restoring mitochondrial function in the hours following treatment.

Following completion and analysis of the above clinical trial, our goal is to use positron emission tomography (PET) scanning in testing the hypothesis that the optimum HBO treatment paradigm improves mitochondrial dysfunction and the energy depletion crisis which occurs following severe TBI in humans. Hovda and colleagues at University of California, Los Angeles (UCLA) have demonstrated a strong correlation between cerebral metabolism and neurological outcome in TBI[93–95]. Clinical improvement coupled to enhanced cerebral metabolism documented by PET scanning would provide strong evidence for the beneficial effect of HBO.

It remains to be seen whether the data accumulated will be compelling enough to institute HBO either alone or in combination with 100% FiO_2 as a standard treatment for severe TBI or whether a multicenter clinical outcome trial will be required. The authors are reasonably confident based on this review and their experience that in either case, HBO will become a significant treatment for patients suffering a severe TBI.

REFERENCES

1 Narayan RK, Michel ME, Ansell B, *et al.* Clinical trials in head injury. *J Neurotrauma* 2002; **19**: 503–557
2 Clifton GL, Miller ER, Choi SE, *et al.* Lack of effect of hypothermia in acute brain injury. *N Engl J Med* 2001; **344**: 556–563
3 Gaab MR, Trost HA, Akantara A, *et al.* 'Ultrahigh' dexamethasone in acute brain injury. Results from a prospective randomized double-blind multicenter trial (GUDHIS). German Ultrahigh Dexamethasone Head Injury Study Group. *Zentralbl Neurochir* 1994; **55**: 135–143
4 Marshall LF, Maas AI, Marshall SB, *et al.* A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. *J Neurosurg* 1998; **89**: 519–525
5 Morris GF, Bullock R, Marshall SB, *et al.* Failure of the competitive N-methyl-D-aspartate antagonist Selfotel (CGS 19755) in the treatment of severe head injury: Results of two phase III clinical trials. The Selfotel Investigators. *J Neurosurg* 1999; **91**: 737–743
6 Rockswold GL, Ford SE, Anderson DL, *et al.* Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. *J Neurosurg* 1992; **76**: 929–934
7 Rockswold SB, Rockswold GL, Vargo JM, *et al.* The effects of hyperbaric oxygen on cerebral metabolism and intracranial pressure in severely brain-injured patients. *J Neurosurg* 2001; **94**: 403–411
8 Tolias CM, Reinert M, Seiler R, *et al.* Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: A prospective historical cohort-matched study. *J Neurosurg* 2004; **101**: 435–444
9 Daugherty WP, Levasseur JE, Sun D, *et al.* Effects of hyperbaric oxygen therapy on cerebral oxygenation and mitochondrial function following moderate lateral fluid-percussion injury in rats. *J Neurosurg* 2004; **101**: 499–504
10 Zhou Z, Daugherty WP, Sun D, *et al.* Hyperbaric oxygen treatment protects mitochondrial function and improves cognitive recovery in rats following lateral fluid percussion injury. *J Neurosurg* 2006; to be published
11 Sukoff MH, Hollin SA, Espinosa OE, *et al.* The protective effect of hyperbaric oxygenation in experimental cerebral edema. *J Neurosurg* 1968; **29**: 236–241
12 Sukoff MH, Ragatz RE. Hyperbaric oxygenation for the treatment of acute cerebral edema. *Neurosurgery* 1982; **10**: 29–38

Published by Maney Publishing (c) W. S. Maney & Son Limited

13 Miller JD, Ledingham IM. Reduction of increased intracranial pressure. *Arch Neurol* 1971; **24**: 210–216
14 Holbach KH, Wassman H, Kolberg T. Verbesserte reversibilität des traumatischen mittelhirnsyndroms bei Anwendung der hyperbaren oxygenierung. *Acta Neurochir* 1974; **30**: 247–256
15 Artru F, Chacornac R, Deleuze R. Hyperbaric oxygenation for severe head injuries: Preliminary results of a controlled study. *Eur Neurol* 1976; **14**: 310–318
16 Graham DI, Adams JH, Doyle D. Ischaemic brain damage in fatal non-missile head injuries. *J Neurol Sci* 1978; **39**: 213–234
17 Bouma GJ, Muizelaar JP, Stringer WA, *et al.* Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. *J Neurosurg* 1992; **77**: 360–368
18 Siesjo BK, Siesjo P. Mechanisms of secondary brain injury. *Eur J Anaesthesiol* 1996; **13**: 247–268
19 Krebs EG. Protein kinases. *Curr Top Cell Regul* 1972; **5**: 99–133
20 Muizelaar JP. Cerebral blood flow, cerebral blood volume, and cerebral metabolism after severe head injury. In: Becker DP, Gudeman SK, eds. *Textbook of Head Injury*, Philadelphia, PA: WB Saunders, 1989: pp. 221–240
21 Waxman SG, Ransom BR, Stys PK. Non-synaptic mechanisms of Ca^{2+}-mediated injury in CNS white matter. *Trends Neurosci* 1991; **14**: 461–468
22 Young W. Role of calcium in central nervous system injuries. *J Neurotrauma* 1992; **9**: S9–S25
23 Siesjo BK. Basic mechanisms of traumatic brain damage. *Ann Emerg Med* 1993; **22**: 959–969
24 Krause GS, Kumar K, White BC, *et al.* Ischemia, resuscitation, and reperfusion: Mechanisms of tissue injury and prospects for protection. *Am Heart J* 1986; **16**: 1200–1205
25 Ikeda Y, Long DM. The molecular basis of brain injury and brain edema: The role of oxygen free radicals. *Neurosurgery* 1990; **27**: 1–11
26 Siesjo BK, Agardh CD, Bengtsson F. Free radicals and brain damage. *Cerebrovasc Brain Metabol Rev* 1989; **1**: 165–211
27 Menzel M, Doppenberg EM, Zauner A, *et al.* Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. *J Neurosurg* 1999; **91**: 1–10
28 Verweij BH, Muizelaar JP, Vinas FC, *et al.* Mitochondria dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111). *Neurol Res* 1997; **19**: 334–339
29 Lifshitz J, Sullivan PG, Hovda DA, *et al.* Mitochondrial damage and dysfunction in traumatic brain injury. *Mitochondrion* 2004; **4**: 1–9
30 Signoretti S, Marmarou A, Tavazzi B, *et al.* N-Acetylaspartate reduction as a measure of injury severity and mitochondrial dysfunction following diffuse traumatic brain injury. *J Neurotrauma* 2001; **18**: 977–991
31 Verweij BH, Muizelaar P, Vinas FC, *et al.* Impaired cerebral mitochondrial function after traumatic brain injury in humans. *J Neurosurg* 2000; **93**: 815–820
32 Bergsneider M, Hovda DA, Shalmon E, *et al.* Cerebral hyperglycolysis following severe traumatic brain injury in humans: A positron emission tomography study. *J Neurosurg* 1997; **86**: 241–251
33 Valadka AB, Goodman JC, Gopinath SP, *et al.* Comparison of brain tissue oxygen tension to microdialysis-based measures of cerebral ischemia in fatally head-injured humans. *J Neurotrauma* 1998; **7**: 509–519
34 Van den Brink WA, Van Santbrink H, Steyerberg EW, *et al.* Brain oxygen tension in severe head injury. *Neurosurg* 2000; **46**: 868–876
35 Zauner A, Doppenberg EM, Woodward JJ, *et al.* Continuous monitoring of cerebral substrate delivery and clearance: Initial experience in 24 patients with severe acute brain injuries. *Neurosurgery* 1997; **41**: 1082–1091
36 De Salles AA, Muizelaar JP, Young HF. Hyperglycemia, cerebrospinal fluid lactic acidosis, and cerebral blood flow in severely head-injured patients. *Neurosurgery* 1987; **21**: 45–50
37 Metzel E, Zimmermann WE. Changes of oxygen pressure, acid-base balance, metabolites and electrolytes in cerebrospinal fluid and blood after cerebral injury. *Acta Neurochir* 1971; **25**: 177–188
38 De Salles AA, Kontos HA, Becker DP, *et al.* Prognostic significance of ventricular CSF lactic acidosis in severe head injury. *J Neurosurg* 1986; **65**: 615–624
39 Murr R, Stummer W, Schürer L, *et al.* Cerebral lactate production in relation to intracranial pressure, cranial computed tomography findings, and outcome in patients with severe head injury. *Acta Neurochir* 1996; **138**: 928–937
40 Robertson CS, Narayan RK, Gokaslan ZL, *et al.* Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. *J Neurosurg* 1989; **70**: 222–230
41 Lambertsen CJ, Kough RH, Cooper DY, *et al.* Oxygen toxicity; effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. *J Appl Physiol* 1953; **5**: 471–486
42 Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. *J Clin Invest* 1948; **27**: 476–483
43 Illingworth C. Treatment of arterial occlusion under oxygen at two atmospheres pressure. *Br Med J* 1962; **2**: 1271–1275
44 Smith G, Lawson S, Renfrew I, *et al.* Preservation of cerebral cortical activity by breathing oxygen at two atmospheres of pressure during cerebral ischemia. *Surg Gynec Obstet* 1961; **113**: 13–16
45 Jacobson I, Harper AM, McDowall DG. The effects of oxygen under pressure on cerebral blood flow and cerebral venous oxygen tension. *Lancet* 1963; **2**: 549
46 Tindall GT, Wilkins RH, Odom GL. Effect of hyperbaric oxygenation on cerebral blood flow. *Surg Forum* 1965; **16**: 414–416
47 Saltzmann HA, Smith RL, Fuson HO, *et al.* Hyperbaric oxygenation. *Monogr Surg Sci* 1965; **2**: 1–68
48 Ingvar DH, Lassen, NA. Treatment of focal cerebral ischemia with hyperbaric oxygenation. *Acta Neurol Scand* 1965; **41**: 92–95
49 Whalen RE, Heyman A, Saltzman H. The protective effect of hyperbaric oxygenation in cerebral anoxia. *Arch Neurol* 1966; **14**: 15–20
50 Jacobson I, Lawson DD. The effect of hyperbaric oxygen on experimental cerebral infarction in the dog. *J Neurosurg* 1963; **20**: 849–859
51 Dunn JE, Connolly JM. Effects of hypobaric and hyperbaric oxygen on experimental brain injury. In: Brown IW, Cox BG, eds. *Hyperbaric Medicine*, Washington, DC: National Research Council, 1966: pp. 447–454
52 Sukoff MH, Hollin SA, Jacobson JH. The protective effect of hyperbaric oxygenation in experimentally produced cerebral edema and compression. *Surgery* 1967; **62**: 40–46
53 Moody RA, Mead CO, Ruamsuke S, *et al.* Therapeutic value of oxygen at normal and hyperbaric pressure in experimental head injury. *J Neurosurg* 1970; **32**: 51–54
54 Wüllenweber R, Gött U, Holbach KH. rCBF during hyperbaric oxygenation. In: Brock M, Fieschi C, Ingvar DH, Lassen NA, Schiirmann K, eds. *Cerebral Blood Flow*, Berlin: Springer-Verlag, 1969: pp. 270–272
55 Mogami H, Hayakawa T, Kanai N, *et al.* Clinical application of hyperbaric oxygenation in the treatment of acute cerebral damage. *J Neurosurg* 1969; **1**: 636–643
56 Hayakawa T, Kanai N, Kuroda R, *et al.* Response of cerebrospinal fluid pressure to hyperbaric oxygenation. *J Neurol Neurosurg Psychiatry* 1971; **34**: 580–586
57 Miller JD, Fitch W, Ledingham IM, *et al.* The effect of hyperbaric oxygen on experimentally increased intracranial pressure. *J Neurosurg* 1970; **33**: 287–296
58 Holbach KH, Schröder FK, Köster S. Alterations of cerebral metabolism in cases with acute brain injuries during spontaneous respiration of air, oxygen and hyperbaric oxygen. *Eur Neurol* 1972: **8**: 158–160
59 Holbach KH. Effect of hyperbaric oxygenation (HO) in severe injuries and in marked blood flow disturbances of the human brain. In: Schürmann K, ed. *Advances in Neurosurgery*, Vol. 1, Berlin: Springer, 1973: pp. 158–163

Published by Maney Publishing (c) W. S. Maney & Son Limited

60 Holbach KH, Caroli A, Wassmann H. Cerebral energy metabolism in patients with brain lesions of normo- and hyperbaric oxygen pressures. *J Neurol* 1977; **217**: 17–30

61 Artru F, Philippon B, Gau F, *et al.* Cerebral blood flow, cerebral metabolism and cerebrospinal fluid biochemistry in brain-injured patients after exposure to hyperbaric oxygen. *Eur Neurol* 1976; **14**: 351–364

62 Contreras FL, Kadekaro M, Eisenberg HM. The effect of hyperbaric oxygen on glucose utilization in a freeze traumatized rat brain. *J Neurosurg* 1988; **68**: 137–141

63 Mink RB, Dutka AJ. Hyperbaric oxygen after global cerebral ischemia in rabbits reduces brain vascular permeability and blood flow. *Stroke* 1995; **26**: 2307–2312

64 Siddiqui A, Davidson JD, Mustoe TA. Ischemic tissue oxygen capacitance after hyperbaric oxygen therapy: A new physiologic concept. *Plast Reconstr Surg* 1997; **99**: 148–155

65 Obrist WD, Langfitt TW, Jaggi JL, *et al.* Cerebral blood flow and metabolism in comatose patients with acute head injury. *J Neurosurg* 1984; **61**: 241–253

66 Robertson CS, Contant CF, Gokaslan ZL, *et al.* Cerebral blood flow, arteriovenous oxygen difference, and outcome in head injured patients. *J Neurol Neurosurg Psychiatry* 1992; **55**: 594–603

67 Dixon CE, Lyeth BG, Povlishock JT, *et al.* A fluid percussion model of experimental brain injury in the rat. *J Neurosurg* 1987; **67**: 110–119

68 McIntosh TK, Vink R, Noble L, *et al.* Traumatic brain injury in the rat: Characterization of a lateral fluid-percussion model. *Neuroscience* 1989; **28**: 233–244

69 Levasseur JE, Alessandri B, Reinert M, *et al.* Fluid percussion injury transiently increases then decreases brain oxygen consumption in the rat. *J Neurotrauma* 2000; **17**: 101–112

70 Azbill RD, Mu X, Bruce-Keller AJ, *et al.* Impaired mitochondrial function, oxidative stress and altered antioxidant enzyme activities following traumatic spinal cord injury. *Brain Res* 1997; **765**: 283–290

71 Springer JE, Azbill RD, Carlson SL. A rapid and sensitive assay for measuring mitochondrial metabolic activity in isolated neural tissue. *Brain Res Brain Res Protoc* 1998; **2**: 259–263

72 Bullock RM, Mahon R. Hypoxia and traumatic brain injury. *J Neurosurg* 2006; **104**: 170–172

73 Rockswold GL, Ford SE, Anderson JR, *et al.* Patient monitoring in the monoplace hyperbaric chamber. *Hyperb Oxygen Rev* 1985; **6**: 161–168

74 Weaver LK, Greenway L, Elliot CG. Performance of the Sechrist 500A hyperbaric ventilator in a monoplace hyperbaric chamber. *J Hyperb Med* 1988; **3**: 215–225

75 Weaver LK. Management of critically ill patients in the monoplace hyperbaric chamber. In: Kindwall EP, Whelan HT, eds. *Hyperbaric Medicine Practice*, 2nd edn, Flagstaff, AZ: Best Publishing Company, 1999: pp. 245–279

76 Weaver LK. Operational use and patient monitoring in the monoplace chamber. *Respir Care Clin Nh Am* 1999; **5**: 51–92

77 Klein J. Normobaric pulmonary oxygen toxicity. *Anesth Analg* 1990; **70**: 195–207

78 Wispe JR, Roberts RJ. Molecular basis of pulmonary oxygen toxicity. *Clin Perinatol* 1987; **14**: 651–656

79 Mantell LL, Horowitz S, Davis JM, *et al.* Hyperoxia-induced cell death in the lung – the correlation of apoptosis, necrosis, and inflammation. *Ann NY Acad Sci* 1999; **887**: 171–180

80 DeForge LE, Preston AM, Takeuchi E, *et al.* Regulation of interleukin-8 gene expression by oxidant stress. *J Biol Chem* 1993; **268**: 25568–25576

81 Deaton PR, McKellar CT, Culbreth R, *et al.* Hyperoxia stimulates interleukin-8 release from alveolar macrophages and U937 cells: Attenuation by dexamethasone. *Am J Physiol* 1994; **267**: L187–L192

82 Muehlstedt SG, Richardson CJ, Lyte M, *et al.* Cytokines and the pathogenesis of nosocomial pneumonia. *Surgery* 2001; **130**: 602–609

83 Bardin H, Lambertsen CJ. A quantitative method for calculating pulmonary toxicity: Use of the unit of pulmonary toxicity dose (UPTD). Institute for Environmental Medicine Report, Philadelphia, PA: University of Pennsylvania, 1970

84 Wright WB. Use of the University of Pennsylvania Institute for Environmental Medicine procedure for calculation of cumulative pulmonary oxygen toxicity. Report 2-72, Washington, DC: US Navy Experimental Diving Unit, 1972

85 Demopoulos HB, Flamm E, Seligman M, *et al.* Oxygen free radicals in central nervous system ischemia and trauma. In: Autor AP, ed. *Pathology of Oxygen*, New York: Academic Press, 1982: pp. 127–155

86 Demopoulos HS, Flamm ES, Seligman ML, *et al.* Further studies on free-radical pathology in the major central nervous system disorders: Effect of very high doses of methylprednisolone on the functional outcome, morphology, and chemistry of experimental spinal cord impact injury. *Can J Physiol Pharmacol* 1982; **60**: 1415–1424

87 Ortega BD, Demopoulos HB, Ransohoff J. Effect of antioxidants on experimental cold-induced cerebral edema. In: Reulen HJ, Schurmann K, eds. *Steroids and Brain Edema*, New York: Springer-Verlag, 1972: pp. 167–175

88 Harabin AL, Braisted JC, Flynn ET. Response of antioxidant enzymes to intermittent and continuous hyperbaric oxygen. *J Appl Physiol* 1990; **69**: 328–335

89 Noda X, McGeer PL, McGeer EML. Lipid peroxide distribution in brain and the effect of hyperbaric oxygen. *J Neurochem* 1983; **40**: 1329–1332

90 Puglia CD, Loeb GA. Influence of rat brain superoxide dismutase inhibition by diethyldithiocarbamate upon the rate of development of central nervous system oxygen toxicity. *Toxicol Appl Pharmacol* 1984; **75**: 258–264

91 Montine TJ, Beal MF, Cudkowicz ME, *et al.* Increased CSF F2-isoprostane concentration in probable AD. *Neurology* 1999; **52**: 562–565

92 Pratico D, Barry OP, Lawson JA, *et al.* IPF2alpha-I: An index of lipid peroxidation in humans. *Proc Natl Acad Sci USA* 1998; **95**: 3449–3454

93 Hattori N, Huang SC, Wu HM, *et al.* Correlation of regional metabolic rates of glucose with Glasgow Coma Scale after traumatic brain injury. *J Nucl Med* 2003; **44**: 1709–1716

94 Glenn TC, Kelly DF, Boscardin WJ, *et al.* Energy dysfunction as a predictor of outcome after moderate or severe head injury: Indices of oxygen, glucose, and lactate metabolism. *J Cereb Blood Flow Metab* 2003; **23**: 1239–1250

95 Vespa PM, McArthur D, O'Phelan K, *et al.* Persistently low extracellular glucose correlates with poor outcome six months after human traumatic brain injury despite a lack of increased lactate: A microdialysis study. *J Cereb Blood Flow Metab* 2003; **23**: 865–877

Published by Maney Publishing (c) W. S. Maney & Son Limited