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Brain Tissue Oxygen Monitoring and Hyperoxic Treatment in Patients with Traumatic Brain Injury

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Abstract

Cerebral ischemia is a well-recognized contributor to high morbidity and mortality after traumatic brain injury (TBI). Standard of care treatment aims to maintain a sufficient oxygen supply to the brain by avoiding increased intracranial pressure (ICP) and ensuring a sufficient cerebral perfusion pressure (CPP). Devices allowing direct assessment of brain tissue oxygenation have showed promising results in clinical studies, and their use was implemented in the Brain Trauma Foundation Guidelines for the treatment of TBI patients in 2007. Results of several studies suggest that a brain tissue oxygen–directed therapy guided by these monitors may contribute to reduced mortality and improved outcome of TBI patients. Whether increasing the oxygen supply to supraphysiological levels has beneficial or detrimental effects on TBI patients has been a matter of debate for decades. The results of trials of hyperbaric oxygenation (HBO) have failed to show a benefit, but renewed interest in normobaric hyperoxia (NBO) in the treatment of TBI patients has emerged in recent years. With the increased availability of advanced neuromonitoring devices such as brain tissue oxygen monitors, it was shown that some patients might benefit from this therapeutic approach. In this article, we review the pathophysiological rationale and technical modalities of brain tissue oxygen monitors, as well as its use in studies of brain tissue oxygen–directed therapy. Furthermore, we analyze hyperoxia as a treatment option in TBI patients, summarize the results of clinical trials, and give insights into the recent findings of hyperoxic effects on cerebral metabolism after TBI.

Keywords: brain tissue oxygenation; neuromonitoring; therapeutic hyperoxia; traumatic brain injury

Introduction

Traumatic brain injury is a leading cause of morbidity and mortality, especially among those under 45 years of age. Although developments in critical care have led to improved treatment of head-injured patients, the damage to the central nervous system often results in an unfavorable outcome. In addition to the initial mechanically-induced brain tissue injury, the lack of a sufficient oxygen supply to brain tissue is considered a major cause for the development of secondary brain damage. Factors potentially causing the exacerbation of secondary brain damage such as reduced cerebral perfusion pressure (CPP) have been identified, and efforts in clinical practice aim to reduce their effects (Chesnut, 1995). Devices that are capable of measuring the oxygenation of damaged brain tissue or tissue at risk have been developed, and offer extended monitoring options in these patients. Studies have shown that brain tissue oxygenation closely correlates with several outcome parameters and patient prognosis (Chang et al., 2009; Narotam et al., 2009; Spiotta et al., 2010; Stiefel et al., 2005). Applying therapeutic interventions to keep brain tissue oxygenation above certain thresholds might improve mortality and neurological outcome in TBI patients.

Increased interest in therapeutic hyperoxia—the elevation of blood oxygen to supraphysiological levels under normobaric (NBO) or hyperbaric (HBO) conditions—has grown in recent years (Alves et al., 2004; Stover, 2008; Vespa, 2008). *In vivo* imaging and other techniques such as cerebral microdialysis have revealed new insights into the effects of hyperoxia on brain metabolism, and experimental results of this therapeutic approach have been promising (Nortje et al., 2008; Reinert et al., 2004, Rockswold et al., 2010; Rogatsky et al., 2005; Tolias et al., 2004; Vlodavsky et al., 2006; Wang et al., 2010). Nevertheless, a clear benefit for patients must be proven before this therapeutic strategy can be used in clinical practice. As oxygen itself has harmful properties (e.g., vasoconstriction and the formation of reactive oxygen species and radicals), an excessive supply could theoretically aggravate cerebral injuries.

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It has been hypothesized that devices for monitoring brain tissue oxygenation are suitable tools to develop a brain tissue oxygen–directed approach to therapeutic hyperoxia. In this review we give an overview of the rationale of monitoring brain tissue oxygenation, the techniques involved, and give insights into the results of studies of brain tissue oxygen–directed therapy. Furthermore, we analyze the strategy of therapeutic hyperoxia, and summarize studies which have examined the impact of HBO and NBO on TBI patients.

Cerebral Oxygen Supply and Metabolism

The brain receives 20% of the cardiac output of blood, although its weight is on average only about 2% of the body's weight. This outstanding demand makes it highly susceptible to a lack of sufficient blood and oxygen supply with subsequent development of cellular hypoxia. Oxygen is inhaled and then transported from the lungs to the brain tissue within the bloodstream. Under normal atmospheric pressure most of the oxygen is bound to hemoglobin and the fraction of dissolved oxygen is very small. At the macroscopic level, the cardiovascular and respiratory systems as well as the amount of hemoglobin play major roles in maintaining the brain's oxygen supply. The oxygen is unloaded from red blood cells into the periphery according to the status of the hemoglobin dissociation curve. The form of this curve is unique and allows easy binding of oxygen to hemoglobin in the lungs, and easy dissolving in the peripheral tissues. The value of pH as well as temperature influence the status of the curve, so a shift of the curve to the right due to increasing acidity in the blood after passage through the tissues results in higher oxygen emission by red blood cells. Oxygen diffusion from capillaries to tissue occurs radially, and was described by Krogh (1919) in a simplified model in which capillaries are arranged in a parallel manner with each capillary supplying a cylindrical tissue volume (Fig. 1). Oxygen content is high at the proximal capillaries and decreases linearly. Fick's laws of diffusion state that the rate of oxygen diffusion is directly proportional to the tension gradient (in the brain this means partial arterial oxygen pressure [Pao_2] minus partial oxygen pressure in the brain [$PBRO_2$]). According to the model of Krogh, the area of oxygen supply is increased if oxygen tension is high. If oxygen tension in capillaries is increased, such as with therapeutic hyperoxia, a larger proportion of brain tissue surrounding the capillary is supplied with oxygen. Kuschinsky and Paulson (1992) hypothesized that the oxygen supply to the brain does not depend solely on passive oxygen diffusion from a distinct number of capillaries as proposed by the model of Krogh. This theory is supported by the findings of Jespersen and Ostergaard (2012), who published a model of cerebral oxygen extraction that demonstrates that the capillary diffusion capacity depends on tissue oxygen tension, as well as capillary transit time heterogeneity. Cerebral blood flow (CBF) also plays a distinct role in maintaining the brain's oxygen supply. Autoregulatory systems of the brain aim to keep global CBF constant, given the mean arterial blood pressure is within the physiological range from 50–150 mm Hg. Within an intact autoregulatory system, local CBF is also adjusted in order to meet the demand of distinct areas, or to decrease a surplus of oxygen delivery. The ratio of cerebral oxygen consumption to cerebral oxygen delivery is defined by the oxygen extraction fraction (OEF), and is approximately 0.4 in healthy individuals (Derdeyn et al., 2002). If CBF falls below a critical threshold, the OEF is increased to meet the brain tissue's oxygen demand. Severe disturbances of those autoregulatory systems are known to occur in disorders of the brain such as stroke and trauma, contributing to pathophysiological derangements of cerebral metabolism. Menon and colleagues (2004) studied 13 patients with moderate and severe TBI undergoing $PBRO_2$ monitoring, repetitive positron emission tomography (PET) scanning, and electron microscopy of pericontusional tissue harvested during surgical procedures. Following baseline PET scanning, a hyperventilation intervention was performed, resulting in a decrease of partial

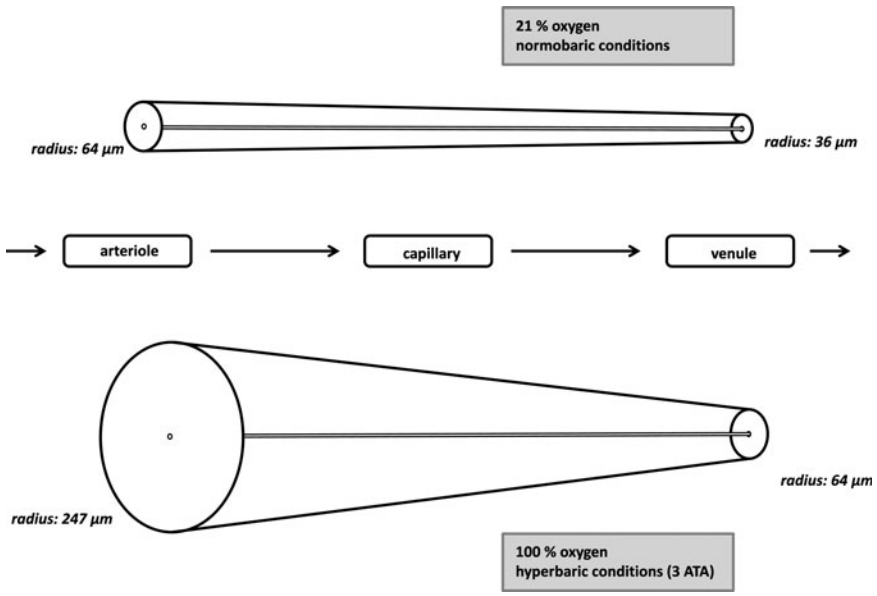

FIG. 1. The cylindrical model described by Krogh (1919) demonstrates the association of oxygen tension and diffusion area in capillaries.

arterial carbon dioxide pressure [$Paco_2$] to 30 mm Hg, while jugular venous oxygen saturation ($Sjvo_2$) was kept above 50%. Brain tissue was classified as hypoxic or normoxic, depending on the $Pbro_2$ values (the cutoff value was set at 10 mm Hg). PET scanning was repeated and revealed a significant reduction in regional CBF and $Pbro_2$ in hypoxic as well as in normoxic brain regions. This resulted in a significant increase in OEF. However, hypoxic brain regions achieved significantly smaller OEF increases compared to normoxic brain regions (percentage change OEF: 7% versus 16%, respectively), and microscopic examination of hypoxic brain tissue showed endothelial swelling, microvascular collapse, and perivascular edema, which are possible explanations for the failure of autoregulatory systems.

The oxygen delivered to cells is used in the aerobic metabolism of glucose through oxidative phosphorylation utilizing energy in form of adenosine triphosphate (ATP). The enzymatic reactions involved are localized in the mitochondria of brain cells. The cerebral metabolic rate of oxygen ($CMRO_2$) reflects this function of mitochondrial activity. Under normal conditions, the normal value in humans is approximately 3.3 mL/100 mL/min (Ito et al., 2005). If there is a significant reduction of CBF or Pao_2 levels fall below ischemic thresholds, $CMRO_2$ is decreased, indicating a shift from aerobic to anaerobic metabolism.

Pathophysiological changes in cerebral oxygen metabolism after traumatic brain injury

The damage to brain parenchyma caused by TBI is divided into two categories: Focal lesions (e.g., contusions and hemorrhage), caused by direct contact, and global (diffuse) lesions caused by acceleration/deceleration resulting in brain edema and diffuse axonal injury (Werner and Engelhard, 2007). Brain tissue damaged directly at initial trauma is classified as primary brain damage. It is considered irreversible damage to the brain, and therefore is not amenable to neuroprotective therapies. In contrast, secondary brain damage develops through pathological processes in the brain during the time period after the initial trauma. Although these pathological processes have not yet been fully elucidated, secondary brain damage can be influenced by therapeutic interventions, and is the primary objective of current research activities in the field of TBI.

Available data suggest that cerebral ischemia plays a key role in the development of secondary brain damage (Coles, 2004; Werner and Engelhard, 2007). In fact, post-mortem analysis of brain trauma victims showed signs of cerebral tissue infarction in 90% of cases (Graham et al., 1989). The critical threshold for CBF in TBI is considered to be 15 mL/100 mL/min (Cunningham et al., 2005), and alterations in CBF occur in the majority of patients with TBI. Cerebral ischemia after TBI leads to several pathophysiological alterations of cerebral metabolic pathways. The first, acute phase is mainly affected by impaired regulation of CBF, while later stages of the pathophysiological ischemic cascade are characterized by inflammatory processes, finally leading to necrotic or apoptotic cell death.

If ischemia occurs in brain tissue, anaerobic metabolism leads to an accumulation of pyruvate, which is used to regenerate cytoplasmic NADH from NAD^+ via lactate dehydrogenase (anaerobic glycolysis). Increased production of lactate results in local acidosis. Ion hemostasis is disturbed, since active transporters, such as the Na^+-K^+-ATPase transporter, have a high demand for ATP. It is well recognized that cerebral hyperglycolysis commonly occurs after TBI (Bergsneider et al., 1997), and the results of several studies suggest that activation of glucose transporter systems influences cerebral oxygen consumption (Holbein et al., 2009). This may represent a protective mechanism of the brain, as a PET study of TBI patients revealed that brain regions with low OEF were associated with reductions in cerebral glucose metabolism (Abate et al., 2008). Importantly, cerebral hyperglycolysis also occurs in the absence of hypoxia. Cesarini and associates (2002) showed that in patients with aneurysmal subarachnoid hemorrhage and microdialysis monitoring, decreased extracellular concentrations of glucose, and balanced increases in lactate and pyruvate concentrations, were associated with a favorable outcome. Oddo and colleagues (2012) demonstrated that elevated concentrations of cerebral lactate in patients with subarachnoid hemorrhage were more often attributable to aerobic hyperglycolysis than to brain hypoxia (median: 78% versus 11%). Cerebral hyperglycolytic lactate predicted good recovery in these patients, supporting the hypothesis that lactate may also have neuroprotective properties in brain ischemia (Berthet et al., 2009). Cerebral hyperglycolysis in the recovery phase after TBI has been discussed as a mechanism of the brain to encounter the extreme metabolic demand and restore cerebral hemostasis (Cesarini et al., 2002). Therefore, increased production of cerebral lactate in TBI may indicate anaerobic metabolism, as well as cerebral hyperglycolysis augmenting the brain cells' energy supply. Persistent anaerobic metabolism leads to accumulation of sodium and chloride ions in the cell, leading to development of edema through osmotic water influx. In the subsequent phases of the ischemic cascade, cellular mediators including proinflammatory cytokines, prostaglandins, and free radicals are released, which induce chemokines and adhesion molecules. These inflammatory processes lead to infiltration of the injured tissue by cells of the immune system such as macrophages and T lymphocytes. Within hours to weeks, the injured tissue is replaced by scar tissue through production of microfilaments and neutropins by astrocytes (Werner and Engelhard, 2007).

Importantly, neural cells and mitochondria have effective mechanisms to cope with reduced oxygen supply. Experimental studies have shown that values of intracellular oxygen tension as low as 0.2 mm Hg enable mitochondria to sustain cellular respiration (Scheufler et al., 2002). In thromboembolic stroke, the widely accepted concept of the penumbra describes brain tissue which is impaired in functional activity due to an insufficient oxygen supply, but not irreversibly damaged (Fisher, 2004). Although there are substantial differences in the pathophysiology of ischemic stroke and TBI, there is increasing evidence for the existence of a "traumatic penumbra" (Abate et al., 2008; Coles et al., 2004). This brain tissue, also called "tissue at risk," is most likely to suffer irreversible damage. Monitoring brain tissue oxygenation helps clinicians initiate adequate action when episodes of cerebral hypoxia in this tissue are identified.

Monitoring brain tissue oxygenation

There are several methods described to measure brain tissue oxygenation. Measurement of $SjvO_2$ is a bedside

technique allowing measurement of global brain oxygen saturation. An association between $Sjvo_2$ and poor neurologic outcome has been described (Cruz, 1998; Robertson et al., 1995), but its major limitation is the inability to detect focal cerebral ischemic lesions. Moreover, a study using PET showed that 13% of the brain has to be ischemic before $Sjvo_2$ falls below 50% (Coles et al., 2004). Kiening and colleagues (1996) demonstrated that measurement of local oxygenation by $PBRO_2$ probes is more suitable for long-term monitoring than measurement of $Sjvo_2$. For this continuous direct measurement of brain tissue oxygenation, a fine catheter is inserted into the brain parenchyma during an operation after craniotomy or through a specially-designed bolt (Fig. 2). The placement site of the probe is important, since the data are collected from tissue surrounding the tip of the catheter. The devices most widely used today use two different techniques. One is based on the Clark principle (Fig. 3), and the other is based on an optical technique (Fig. 4). The Clark-based device consists of a membrane covering a layer of electrolyte and two metallic electrodes. Oxygen molecules diffuse through a diffusible membrane and are reduced by a closed gold polarographic cathode. This induces a flow of electric current directly proportional to oxygen concentration. Devices based on the optical technique consist of optical sensors that measure concentrations of substances by wavelength analysis. Oxygen molecules induce photochemical reactions, and thereby change optical properties of indicator compounds.

The device most widely used is the Licox® probe, distributed by Integra Neurosciences (Plainsboro, NJ). It is a Clark-based device and several studies have confirmed its safety and reliability in clinical studies (Dings et al., 1998; Maloney-Wilensky et al., 2009). In 292 patients monitored with this device, only two adverse events (two iatrogenic hematomas not requiring surgical evacuation) were reported. Originally developed for continuous blood gas monitoring, the Paratrend 7 (Diametrics Medical Inc., St. Paul, MN) was also used to measure brain tissue oxygenation (Hutchinson et al., 2000). Based on the Clark principle, $PBRO_2$ measurements could be monitored simultaneously, in addition to partial carbon dioxide pressure in the brain ($PBRCO_2$), pH, and temperature. The optical technique-based Neurotrend® was introduced in 1999 and was used in several studies (Gupta et al., 2002; Johnston et al., 2003). Nevertheless, the Neurotrend and Paratrend® catheters are no longer commercially available since production was discontinued in 2004 (Haitsma et al., 2008). Raumedic (Muenchberg, Germany) recently introduced the optical technique-based Neurovent-TO® and Neurovent-PTO® probes, with combined assessment of temperature, $PBRO_2$, and ICP (PTO). Results from preclinical *in vitro* and *in vivo* experiments have been promising (Orakcioglu et al., 2010; Purins et al., 2010), and some initial cases of its clinical use have been reported (Dengler et al., 2011; Huschak et al., 2009). Another optical-technique probe used in experimental studies on brain tissue oxygenation is the OxyLite® sensor, developed and distributed by Oxford Optronix (Oxford, U.K.; Doll et al., 2009; Nwaigwe et al., 2000). Due to technical differences, measured values cannot be compared directly if different sensor types are used. For example, differences are apparent regarding the sampling surface area and oxygen-sensing section of catheters. The limited reading surface area of the Licox catheter tip is approximately 7–17 mm^2 (Dings et al., 1998; Kiening et al., 1996). The latest generation of Licox catheters (the PMO catheter) has a reading surface area of 18 mm^2, and an oxygen-sensing length of 7 mm. In contrast, the oxygen-sensing section of the Neurotrend catheter has a length of only 1.4 mm (Bader, 2006). As mentioned above, the placement site of the catheter is important for data interpretation, since these devices represent a local technique of neuromonitoring. After TBI, distinct pathophysiological differences are apparent between injured, normal, and at risk brain tissue, so a clear differentiation has to be made between global and focal cerebral metabolism (e.g., if a catheter is placed in contused brain tissue). Additionally, values of CBF differ between the cerebral cortex and subcortical white matter (Reich and Rusinek, 1989), so insertion depth also has an impact on the values obtained. The importance of neuromonitoring probe location is well recognized, and this issue has recently been investigated in two studies. Engstrom and colleagues (2005) demonstrated that the results obtained with cerebral microdialysis analysis catheters depend on their

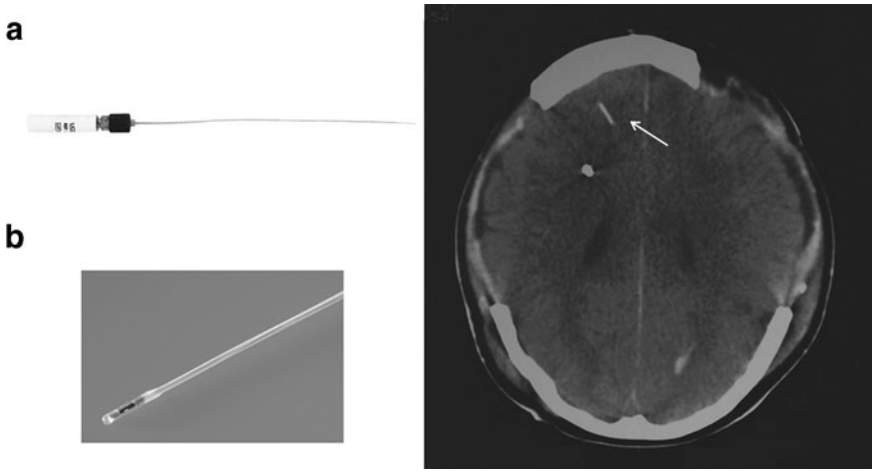

FIG. 2. Left: Catheters for monitoring brain tissue oxygenation (**a**, Licox (r) catheter; **b**, Neurovent-TO® catheter). Right: Computed tomography scan of a patient with traumatic brain injury shows the tip of a Licox probe in the right frontal lobe (arrow).

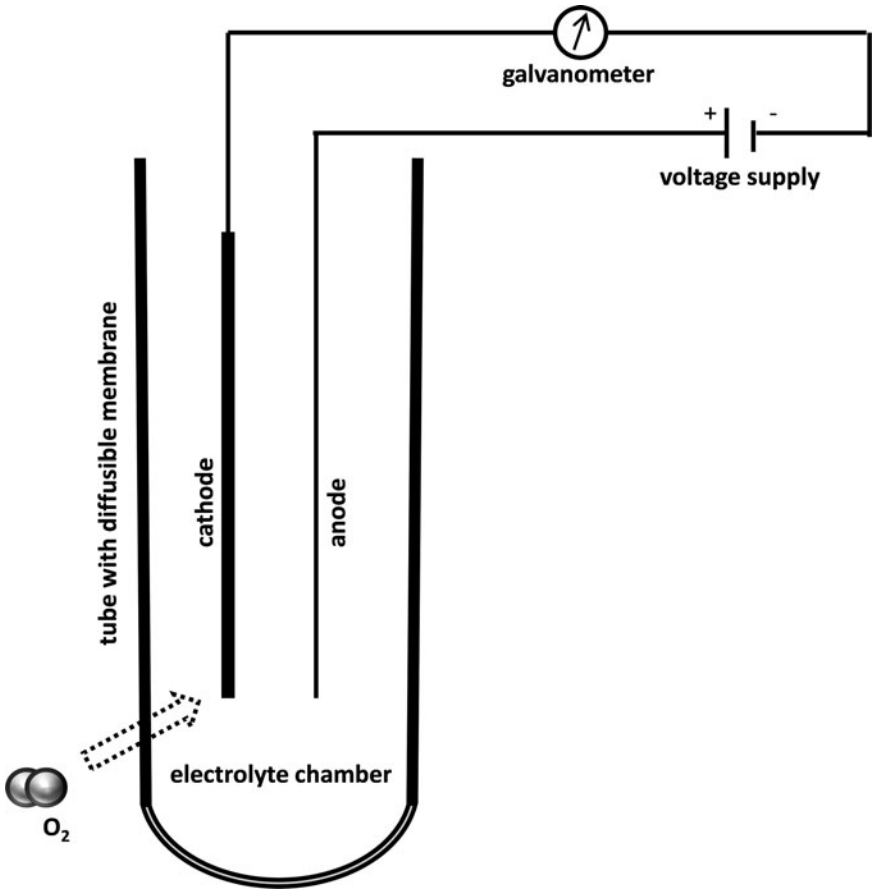

FIG. 3. The Clark electrode measures oxygen on a catalytic surface. This technique is oxygen-consuming, but this has no impact in clinical practice.

placement site. A total of 40 microdialysis catheters were implanted in 22 patients with severe TBI, and all biochemical variables except pyruvate differed significantly between perihemorrhagic tissue and normal tissue of the ipsilateral or contralateral brain hemispheres. Ponce and associates (2012) studied the effects of P_{BRO_2} probe location on the relationship between P_{BRO_2} and neurological outcome in 405 patients with severe TBI. Mean values of P_{BRO_2} were significantly higher in normal brain tissue (30.8 ± 18.2 mm Hg) than in abnormal brain tissue (25.6 ± 14.8 mm Hg). When P_{BRO_2} probes were

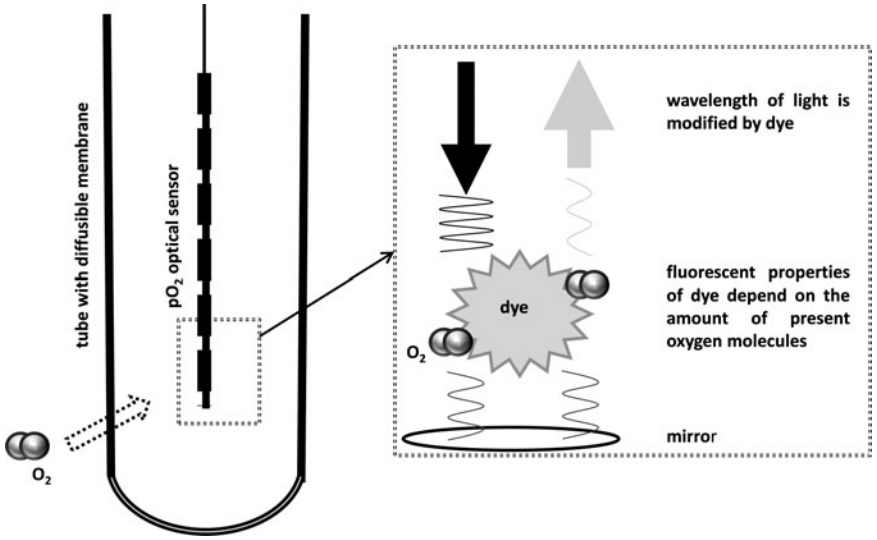

FIG. 4. With optical techniques, wavelength alterations by indicator compounds are registered by optical sensors. The presence of oxygen molecules changes optical properties of these compounds. In contrast to the Clark electrode, this technique does not consume oxygen.

placed in abnormal brain tissue, patients with a favorable outcome had a higher average P_{BRO_2} (28.8 ± 12 mm Hg) than patients with an unfavorable outcome (19.5 ± 13.7 mm Hg). Importantly, no relationship was observed between P_{BRO_2} and outcome if the probes were placed in normal brain tissue.

The P_{BRO_2} value read by the sensor is an integration of measurements of all microvascular compounds of the area surrounding the catheter tip. Therefore the readings are largely influenced by the microvascular composition, and are dependent on the dominance of venous or arterial vessels in the studied area. Under normal circumstances arterial P_{O_2} is about 90 mm Hg, and cerebral venous P_{O_2} is about 35 mm Hg, hence a broad spectrum of values rather than a typical brain tissue PO_2 level is apparent in the brain (Alves et al., 2004). The proportion of venous vessels in the cortical microvasculature is more than 70%, therefore it is assumed that brain P_{BRO_2} mainly reflects venous P_{O_2} (Scheufler et al., 2002). Kiening and associates (1996) found that at a threshold of 50% Sjv_{O_2}, P_{BRO_2} was within the range of 3–12 mm Hg, with a regression curve best fit value of 8.5 mm Hg. While the absolute threshold for P_{BRO_2} probably depends on a range of factors (e.g., precondition, duration, location, tissue condition, and sensor type), it was shown by Sarrafzadeh and colleagues (2003) that impending hypoxia ($P_{BRO_2} < 15$ mm Hg) leads to a gradual increase of glutamate, while parameters of glucose metabolism remain unimpaired. With manifest tissue hypoxia ($P_{BRO_2} < 10$ mm Hg), both lactate and glutamate increase significantly. In practical terms, P_{BRO_2} values of 10–20 mm Hg have been suggested as a threshold for initiating measures to raise brain tissue oxygenation (McCarthy et al., 2009; Meixensberger et al., 2003; Nangunoori et al., 2011; Narotam et al., 2009; Spiotta et al., 2010).

Shortly after the introduction of new brain tissue oxygen monitoring devices, several reports clearly demonstrated their impact on the treatment of head-injured patients. Stiefel and colleagues (2005) implanted brain tissue oxygen monitors in 25 patients with severe TBI, and demonstrated that cerebral hypoxia occurred in patients, even though standard guidelines were followed. Brain tissue oxygen was as low as < 10 mm Hg in 29% of patients with an ICP < 25 mm Hg, and in 27% of patients with a CPP > 60 mm Hg. The mortality rate was higher in patients with reduced brain tissue oxygenation. Consistent with these findings, Chang and coworkers (2009) demonstrated in their study of 27 patients with severe TBI that episodes of low brain oxygen content below 20 mm Hg occur frequently, and are independent of ICP. Several studies have demonstrated that brain hypoxia below 10 mm Hg is associated with worse outcomes after TBI (Bardt et al., 1998; Kiening et al., 1997). Van den Brink and colleagues (2000) demonstrated that the mortality rate was over 50% for patients with brain tissue oxygenation below 10 mm Hg for more than 30 min. A meta-analysis by Maloney-Wilensky and colleagues (2009) showed that in TBI, patients without brain hypoxia (defined as P_{BRO_2} below 10 mm Hg for more than 15 min) had an unfavorable outcome in 43% of cases. In contrast, patients with brain hypoxia had an unfavorable outcome in 73% of cases.

Management of reduced brain tissue oxygenation

Monitors of P_{BRO_2} should be used in combination with other monitors (e.g., an ICP monitor and a standard ICU monitor). Episodes of reduced brain tissue oxygenation should always be interpreted in context with the results of other vital parameter monitors. Unterberg and colleagues (1997) showed that aggressive hyperventilation leads to a decrease in brain tissue oxygenation, so alteration of ventilation parameters may result in a restoration of P_{BRO_2}. In cases of reduced CPP, treatment modalities to maintain CPP above 60 mm Hg result in an increase of P_{BRO_2}. Even in cases of isolated reduced P_{BRO_2}, several interventions can be effective in restoring brain tissue oxygenation. A recent study by Bohman and associates (2011) analyzed medical interventions used for restoring compromised P_{BRO_2} to a level of > 25 mm Hg. Response rates for reaching this level differed between the used interventions, and were 77% for increasing fraction of inspired oxygen (F_{IO_2}), 70% for administration of sedatives, and 50% for transfusion of packed red blood cells. Treatment of increased ICP was effective in 54% of cases, and in cases of normal ICP with a CPP below 60 mm Hg, CPP augmentation using vasopressors was effective in 75%. Other maneuvers such as administration of intravenous fluids, head repositioning, and airway suctioning, were also effective in restoring P_{BRO_2}, but the number of these interventions was small ($n < 10$) in this study. Interestingly, the overall response rate of patients was associated with outcome. Patients who died ($n = 18$) had a 44% response rate to therapy of decreased P_{BRO_2}, whereas patients who survived ($n = 31$) had a response rate of 71%. Another study retrospectively analyzed episodes of compromised brain tissue oxygenation and the interventions initiated when P_{BRO_2} was below 20 mm Hg (Pascual et al., 2011). The most commonly used interventions were administration of sedatives/vasopressors, repositioning, and increasing F_{IO_2}/positive end-expiratory pressure (PEEP). In the majority of cases, only one or two maneuvers were needed to restore P_{BRO_2}, and no superiority of one intervention or combination over others was observed. It is noteworthy that 44% of episodes of compromised P_{BRO_2} were corrected without specific treatment. Stiefel and colleagues (2004) analyzed the effects of surgical decompressive hemicraniectomy on brain tissue oxygenation. Seven patients with severe TBI and raised ICP despite maximal medical management were included. After surgery, cerebral oxygenation improved from 21.2 ± 13.8 mm Hg to 45.5 ± 25.4 mm Hg, demonstrating an increase of more than 100%. Since the changes in P_{BRO_2} and ICP showed only a modest relationship, these data suggest that decompressive hemicraniectomy is associated with a significant improvement in brain tissue oxygenation.

Further studies are needed to identify the most suitable interventions for restoring P_{BRO_2} in patients with severe TBI. The response rate to interventions seems to depend in part on the metabolic state of the brain, so the role of this response rate has to be further investigated.

Studies of brain tissue oxygen-directed therapy

The impact of monitoring brain tissue oxygenation in TBI victims was recognized early, and it was hypothesized that modifying therapy to keep P_{BRO_2} above certain thresholds (so-called brain tissue oxygen–directed therapy) improves outcome compared to conventional ICP/CPP-based therapy. Adamides and colleagues (2009) published results of a study of 30 TBI patients who underwent monitoring of brain tissue

oxygenation with a Licox probe. Of these, 20 patients were treated to keep P_{BRO_2} above 20 mm Hg. Interventions included ventilation adjustments, increasing CPP, and transfusion of packed red blood cells. The duration of compromised brain tissue oxygenation episodes was significantly decreased in the treatment group, whereas no impact on incidence and depth of these episodes was observed. Outcome analysis at 6 months did not show a significant difference between the treatment and control groups. Martini and colleagues (2009) analyzed 123 patients who underwent P_{BRO_2}/ICP monitoring, and compared their results to those of 506 patients who underwent ICP monitoring only. In patients undergoing P_{BRO_2} monitoring, a sophisticated treatment protocol was applied to keep brain tissue oxygenation above 20 mm Hg. This protocol included head adjustment, temperature management, CPP alterations, transfusion of packed red blood cells, ventilation adjustments, and aggressive ICP treatment. Although no data on long-term outcomes are provided, neurological outcome at discharge (functional independence measure) was worse in the P_{BRO_2} group (7.6 ± 3.0) compared to the ICP-only group (8.6 ± 2.8). In addition, the duration of mechanical ventilation, median hospital length of stay, median hospital cost, and mortality was higher in the P_{BRO_2} group compared to the ICP-only group. The results of these studies have been the subject of intense debate (Defillo, 2010; Grady, 2009), and it was speculated that the higher injury scores (mean admission Glasgow Coma Scale [GCS] score, injury severity score, and head abbreviated injury scale score) in the P_{BRO_2} group might have influenced the results of this observational study. Nevertheless, as a result of this debate, there is urgent need for a prospective, randomized controlled trial to study this question.

Nangunoori and colleagues (2011) recently reviewed the literature regarding studies comparing the impact of brain tissue oxygen–directed therapy to standard ICP/CPP therapy on long-term outcome in TBI patients. Four studies with adequate outcome data to define odds ratios and confidence intervals were identified. Meixensberger and colleagues (2003) included 93 TBI patients undergoing monitoring of P_{BRO_2} with a Licox probe in their study. In 53 of these 93 patients, CPP was altered to keep brain tissue oxygenation above 10 mm Hg. Episodes of brain hypoxia occurred less frequently in this group than in the control group. A trend toward better outcome after 6 months was observed in the Licox group, although it did not reach statistical significance. McCarthy and co-workers (2009) included 145 patients in their study, with 81 patients undergoing monitoring of brain tissue oxygen with a Licox probe. All patients were treated with ICP/CPP-guided therapy according to institutional guidelines, and additionally in the Licox group, oxygenation levels of < 20 mm Hg were treated by optimizing F_{IO_2} and oxygen supply. Outcome assessed according to the Glasgow Outcome Scale (GOS) 3 months after discharge was better for patients in the Licox group (moderate/recovered GOS: 79%), than in the ICP/CPP group (moderate/recovered GOS: 61%), but this difference was not statistically significant. A study by Narotam and colleagues (2009) included 139 patients with TBI, and compared a therapy guided by brain tissue oxygen measurement with an established ICP/CPP-directed protocol. All patients were treated to keep CPP above 60 mm Hg. Additionally, a Licox probe was inserted and in cases of low cerebral oxygenation (the threshold was set at 20 mm Hg), measures were undertaken, including hyperoxia, "triple H therapy" (hypervolemia, hypertension, and hemodilution), vasodilators, and transfusion of packed red blood cells if hemoglobin levels were low. Data of these patients were compared with a historical cohort group at the authors' institution. Compared to the historical cohort group, in these patients outcome on the GOS was improved at 6 months (mean scores of 3.55 ± 1.75 versus 2.71 ± 1.65), and the mortality rate was reduced from 41.5% to 25.9%. Spiotta and colleagues (2010) reported results of a study supporting the above findings. A total of 77 patients with severe TBI underwent a brain tissue oxygen–directed therapy with an ischemia threshold of < 20 mm Hg and intervention modalities including oxygen challenge, increasing CPP, and transfusion of packed red blood cells to keep hemoglobin levels above 10 mg/dL. A decompressive craniectomy was performed in cases of persistently low P_{BRO_2}. This scheme reduced the mortality rate from 45.3% (historical control) to 25.7% (brain tissue oxygen–directed therapy). Additionally, the rate of patients with a favorable outcome based on the GOS 3 months after injury was 40% versus 64.3% (historical control and brain tissue oxygen–directed therapy, respectively).

The results of these studies are summarized in Table 1. The common odds ratio is 2.1 (95% CI 1.3,3.1), suggesting a beneficial effect of brain tissue oxygen–directed therapy on TBI patients. The use of devices for monitoring brain tissue oxygenation was included in the Brain Trauma Foundation's guidelines for the management of severe traumatic brain injury in 2007 (Bratton et al., 2007). Nevertheless, further investigation of the impact of brain tissue oxygen–directed therapy on the treatment of TBI patients is needed, and currently a prospective multicenter randomized controlled trial has started recruiting patients (http://clinicaltrials.gov/ct2/show/NCT00974259). This multicenter trial, led by the University of Texas Southwestern Medical Center, represents the first randomized controlled clinical trial on P_{BRO_2} monitoring, and includes adult patients with severe TBI. The primary goal of this study is to investigate whether a protocol-based brain tissue oxygen–directed therapy results in a reduced fraction of time of critical brain tissue oxygenation below 20 mm Hg. It is hoped that the data obtained through this trial will serve as a basis for the conduct of a Phase III study to evaluate the effects of this therapeutic strategy on the neurological outcome of TBI patients.

Effects of hyperoxia on brain metabolism after traumatic brain injury

Several studies have addressed the issue of brain metabolism parameters altered by normobaric hyperoxia treatment. Although modern techniques such as PET scanning have revealed new insights about brain metabolism, this field has to be further elucidated. In a study of patients with severe TBI undergoing multimodal monitoring (Menzel et al., 1999), including cerebral microdialysis, dialysis lactate levels decreased by 40% in patients treated with 100% oxygen for a period of 6 h. Mean P_{BRO_2} levels were increased by $259 \pm 36\%$. Magnoni and colleagues (2003) studied the effects of hyperoxia on cerebral metabolism in 8 patients with severe TBI and demonstrated a significant reduction of lactate after administration of 100% oxygen for a period of 3 h. Since pyruvate

Table 1. Studies Comparing Brain Tissue Oxygen-Directed Therapy Using Licox Probes to Conventional ICP/CPP-Directed Protocols

Study	n	Study design	Outcome assessment	P_{BRO_2} threshold	Probe location	ICP and P_{BRO_2}-directed therapy		ICP/CPP-directed therapy		Odds ratio (95% CI)
						Unfavorable outcome (%)	Favorable outcome (%)	Unfavorable outcome (%)	Favorable outcome (%)	
McCarthy et al., 2009	111	Prospective non-randomized trial	GOS 3 months	20 mm Hg	Non dominant hemisphere	34 (54%)	29 (46%)	32 (67%)	16 (33%)	1.7 (0.7,3.7)
Meixensberger et al., 2003	91	Retrospective cohort-study	GOS 6 months	10 mm Hg	Most injured hemisphere, frontal lobe	18 (35%)	34 (65%)	18 (46%)	21 (54%)	1.6 (0.6,3.7)
Narotam et al., 2009	166	Retrospective cohort-study	GOS 6 months	20 mm Hg	Normal tissue	44 (35%)	83 (65%)	22 (56%)	17 (44%)	2.4 (1.1,5)
Spiotta et al., 2010	123	Retrospective cohort-study	GOS 3 months	20 mm Hg	Most injured hemisphere, frontal lobe	25 (36%)	45 (64%)	32 (60%)	21 (40%)	2.7 (1.3,5.7)
All	491					121 (39%)	191 (61%)	104 (58%)	75 (42%)	2.1 (1.5,3.1)

GOS, Glasgow Outcome Scale; ICP, intracranial pressure; CPP, cerebral perfusion pressure; P_{BRO_2}, partial oxygen pressure in the brain; CI, confidence interval.

levels also decreased, the lactate:pyruvate ratio did not change, and the authors concluded that hyperoxia might induce an overall suppression of glucose metabolism rather than improve oxygen function. These results may indicate a limited time window for normobaric hyperoxia as a treatment modality in TBI, since hyperoxia was started later than 45 h after trauma. When initiated in the acute phase within 6 h after trauma, NBO increased glucose levels significantly and reduced glutamate and lactate levels, as well as lactate: glucose and lactate:pyruvate ratios. Additionally, a significant reduction of ICP was observed (15.03 mm Hg versus 12.13 mm Hg) with no changes in CPP. A more recent study combining microdialysis studies with oxygen-15 PET (^{15}O-PET) in 11 patients (Nortje et al., 2008) showed variable effects on microdialysis parameters. Although no significant changes of glucose, pyruvate, lactate, and glutamate levels were observed, the lactate:pyruvate ratio was significantly reduced. However, changes in mean levels were small, and the range of individual patients' mean lactate:pyruvate ratio changes was heterogenous. In another study of 8 patients with TBI, Tisdall and colleagues (2008) found an increase of brain tissue oxygen, while the microdialysis lactate concentration was reduced, as was the lactate:pyruvate ratio. The results of these studies are summarized in Table 2. The effects of hyperoxia on microdialysis parameters are heterogenous and remain unclear. Several aspects, such as the duration of hyperoxia, as well as the time window of treatment initiation and the different patterns of brain injuries, seem to be of particular importance. Additionally, the probes were not implanted in a standardized manner, so the positions of microdialysis catheters could have varied significantly among patients in the different studies. The results of a recent study by Vilalta and associates (2011) suggest that the impact of hyperoxia on brain metabolism parameters also depends on the metabolic state prior to hyperoxic treatment. Thirty patients with TBI were included in this study. Probes for monitoring ICP, microdialysis parameters, and brain tissue oxygenation, were placed in the least-injured hemisphere. Patients were divided into two groups: patients with baseline brain lactate ≤ 3 mmol/L (group 1), and patients with baseline brain lactate >3 mmol/L (group 2). A 2-hour hyperoxic challenge with 100% O_2 was carried out and microdialysis parameters as well as changes in brain tissue oxygenation were analyzed. In group 1, no significant changes in metabolic parameters were observed, while brain tissue oxygenation was significantly increased. In contrast, in group 2 hyperoxic treatment improved brain tissue oxygenation, but it also significantly increased glucose levels and decreased the lactate:pyruvate ratio by 11.6% (Table 2). These results indicate that hyperoxic treatment might have beneficial effects on the brain metabolism of some, but not all, TBI patients.

All studies have demonstrated a robust effect of hyperoxia on brain tissue oxygenation, significantly elevating levels from baseline values. The effect of this dramatic increase on brain tissue is unclear, and recent studies have focused on this topic using sophisticated imaging techniques. Diringer and colleagues (2007) have examined the effects of 100% oxygen for a period of 1 h on cerebral metabolism and CBF using PET scanning techniques. Five patients with TBI were included in this study, and no differences were seen in CBF, OEF, and global $CMRO_2$ during the application of 100% oxygen. These

TABLE 2. EFFECTS OF HYPEROXIA ON CEREBRAL METABOLISM

Study	n	Treatment	Time window (post-injury)	Probe location	Effect on glucose	Effect on lactate	Effect on pyruvate	Effect on glutamate	Effect on L:P ratio	Effect on P_{BRO_2}
Menzel et al., 1999	22	100% O_2 (6 h)	18 h after admission	Not reported	↔	↓	n/a	n/a	n/a	↑
Magnoni et al., 2003	8	100% O_2 (3 h)	79 h after injury	Normal tissue	↔	↓	↓	↔	↔	↑
Reinert et al., 2003	20	100% O_2 (6 h)	24 h after injury	Normal tissue, frontal lobe	↔	↓	n/a	n/a	n/a	↑
Tolias et al., 2004	52	100% O_2 (24 h)	6 h after admission	Frontal lobe	↑	↓	↓	↓	↔	↑
Tisdall et al., 2008	8	100% O_2 (1 h)	48 h after injury	Pericontusional tissue	↔	↓	n/a	n/a	↓	↑
Nortje et al., 2008	11	60–80% O_2 (0.85 h)	9 days after injury	Various	↔	↕	↔	↔	↓	↑
Rockswold et al., 2010	21	100% O_2 (3 h)	27 h after injury	Least injured hemisphere, frontal lobe	↔	↕	n/a	n/a	↓	↑
Vilalta et al., 2011	16[a]	100% O_2 (2 h)	126 h after injury	Least injured hemisphere, normal tissue	↔	↕	↔	n/a	↔	↑
	13[b]	100% O_2 (2 h)	126 h after injury	Least injured hemisphere, normal tissue	↑	↕	↔	n/a	↓	↑

[a]Baseline lactate level ≤3 mmol/L prior to hyperoxic treatment.
[b]Baseline lactate level >3 mmol/L prior to hyperoxic treatment.
In contrast, the impact of hyperoxia on parameters of cerebral metabolism, as measured by microdialysis parameters, is not clear and displays a heterogenous picture. Different positions of implanted probes (vital brain versus at-risk tissue versus injured brain) in the different patients of various studies may offer one explanation for this discrepancy. Hyperoxia consistently increases measured brain tissue oxygenetion.
L:P, lactate:pyruvate ratio; n/a, not available.

results suggest a lack of metabolic benefit from hyperoxia for the global brain tissue. Nevertheless, Nortje and colleagues (2008) used ^{15}O-PET scanning and found results indicating that some areas of brain may benefit from hyperoxic treatment. Eleven patients with severe TBI were included in their study. After completing baseline PET scanning, 60–80% oxygen was administered, and following a stabilization period of about 60 min, PET scanning was repeated. Consistent with the findings of Diringer and colleagues (2007), no significant differences were observed in whole brain measurements for CBF, OEF, and $CMRO_2$. Interestingly, in areas in which baseline scans revealed a reduced $CMRO_2$ of less than 37 μmol × 100 mL^{-1} × min^{-1}, hyperoxia increased the $CMRO_2$ from 23 to 30 μmol × 100 mL^{-1} × min^{-1}. No significant changes were observed for CBF and OEF. These results suggest a preferential metabolic benefit with hyperoxia for at-risk tissue.

Figaji and colleagues (2010) studied the effects of hyperoxic challenges of 15 min on 28 children (age < 15 years) with severe TBI. Hyperoxia increased Pao_2 as well as P_{BRO_2} significantly in these patients. The oxygen reactivity index (ΔP_{BRO_2}:ΔPao_2 ratio) was analyzed, and outcome analysis 6 months after injury showed that this index was inversely related to outcome. These findings, together with the results of other studies, are indicative that a patient's response to hyperoxic challenges might reflect, at least to some extent, the presence and severity of metabolic disturbances of the injured brain.

Hyperbaric Oxygen Treatment

If oxygen is inhaled under normal atmospheric pressure, the amount of dissolved oxygen molecules in plasma is low and most of the blood oxygen is bound to hemoglobin. Increasing the amount of inhaled oxygen increases the amount of dissolved oxygen in plasma, but this increase is limited to approximately 10% of the total amount of oxygen in blood when 100% oxygen is inhaled. Inhaling oxygen under increased pressure enables further solution of oxygen in plasma unbound to hemoglobin, therefore the total amount of oxygen in the blood is elevated by approximately 30% when HBO treatment is carried out at a pressure altitude of 3 absolute atmospheres (ATA; Table 3).

Studies of HBO in experimental models of TBI have shown several neuroprotective effects (Daugherty et al., 2004; Palzur et al., 2008; Rogatsky et al., 2005; Vlodavsky et al., 2006; Voigt et al., 2008; Wang et al., 2010; Zhou et al., 2007), resulting in reduced mortality and improved neurological outcomes. Nevertheless, HBO is not yet ready to be implemented in clinical practice, as a clear benefit for patients with TBI remains to be proven. Three clinical trials were carried out to examine the effects of HBO treatment on outcomes of patients with TBI (Artru et al., 1976; Ren et al., 2001; Rockswold et al., 2001; Table 4). Of these, only the study by Rockswold and colleagues meets today's standards of a controlled randomized prospective trial. A total of 168 patients with TBI and a GCS score < 9 were included and were randomized to HBO or standard treatment within 6–24 h after admission. HBO treatment for 1 h was carried out every 8 h for a period of 2 weeks or until the patient followed commands or was pronounced brain dead. Outcome analysis showed a reduction of mortality from 32% to 17% in patients treated with HBO. Subgroup analysis demonstrated

Table 3. Effects of Hyperbaric and Normobaric Oxygen Treatment on Oxygen Content of Blood

	FIO_2	P_{total} lungs	PO_2 lungs	SaO_2 hb	Amount of O_2/hb	Amount of O_2/plasma	Amount O_2/total
Air 1 ATA	21%	713 mmHg	150 mmHg	97%	197 mL/L	4.5 mL/L	201.5 mL/L
NBO 1 ATA	100%	713 mmHg	713 mmHg	100%	201 mL/L	21.4 mL/L	222.4 mL/L
HBO 2 ATA	100%	1473 mmHg	1473 mmHg	100%	201 mL/L	44 mL/L	245 mL/L
HBO 3 ATA	100%	2233 mmHg	2233 mmHg	100%	201 mL/L	67 mL/L	268 mL/L

Under normal atmospheric conditions oxygen is mainly bound to hemoglobin. An increase in inspired oxygen as with normobaric oxygen treatment results in only small changes of oxygen dissolved in blood plasma. In contrast, hyperbaric oxygen treatment can elevate the amount of total oxygen in blood substantially. All values are for an environment with a temperature of 37°C and hemoglobin levels of ~15 g/dL.

ATA, absolute atmosphere; P_{total} total pressure; Po_2, partial oxygen pressure; Sao_2 arterial oxygen saturation; Fio_2, fraction of inspired oxygen; HBO, hyperbaric oxygen; NBO, normobaric oxygen.

that patients with an initial ICP of > 20 mm Hg and with a GCS score of 4–6 had the greatest benefit (mortality reduction from 42% to 17% and 48% to 21%, respectively). Nevertheless, outcome analysis 18 months after trauma did not show any significant differences in GOS scores between groups. Differences between guideline therapies at the time the study was carried out and the guidelines accepted today do not allow a complete comparison to today's situation. Nevertheless, the results of this study do suggest that HBO therapy might be beneficial in the treatment of TBI victims. HBO treatment modalities have to be further investigated since they seem to have a significant impact on the efficacy of this treatment. Results of a study in a rat model of focal cerebral ischemia suggest that application of HBO beyond a time window of 6 h after stroke onset may aggravate histological and clinical ischemic injury due to possible detrimental effects of hyperoxic treatment (Lou et al., 2004).

Rockswold and colleagues (2010) recently published results of a study comparing the effects of HBO and NBO on cerebral metabolism, ICP, and oxygen toxicity in patients with severe TBI. Sixty-nine patients were enrolled and received either standard care treatment, 3 h of NBO, or HBO for 1 h. Lactate:pyruvate ratios were reduced in patients treated with HBO and NBO (10% and 3% compared to control group, respectively), but $CMRO_2$ was significantly increased, by 37% at 6 h after HBO treatment, whereas NBO therapy had no effect on $CMRO_2$ compared to controls. Additionally, HBO therapy reduced elevated ICP compared to controls, while NBO had no impact on ICP. The authors showed that the greatest benefit for cerebral metabolism, especially $CMRO_2$, was achieved when measured brain tissue oxygen exceeded a level of 200 mm Hg. This level was reached in 51% of patients treated with HBO, and in 5% of patients treated with NBO, indicating a more robust effect of HBO treatment than NBO treatment. These results are consistent with findings from experimental studies on ischemic stroke. In a model of transient focal cerebral ischemia, HBO was more effective than prolonged NBO in reducing infarct size and improving functional outcome, although treatment onset of HBO was delayed (Beynon et al., 2007).

Nevertheless, HBO has several disadvantages compared to NBO. Logistical challenges with increased transfer time of patients and limited availability of chambers are major restrictions. In contrast, NBO therapy could be initiated earlier after trauma by emergency medical personnel with only minimal risk. Further studies on both treatment modalities are needed, and perhaps the sequential administration of both therapies will prove to have a positive impact on the clinical course of patients with TBI.

Side effects of hyperoxic treatment

Several side effects of hyperoxia are known and this has to be considered when discussing hyperoxic treatment with NBO or HBO as an option in patients with TBI. Hyperoxia is associated with systemic side effects on the lungs, heart, and gastrointestinal tract (Bostek, 1989). It is assumed that lung damage is caused by a high production of reactive oxygen species (ROS; Pagano and Barazzone-Argiroffo, 2003). In healthy individuals, inhalation of 95% oxygen leads to tracheobronchitis within 4–22 h, but terminating inhalation results in complete resolution of symptoms within a few days (Clark and Lambertsen, 1971). In animals exposed to prolonged hyperoxia, histopathological analysis of lung tissue showed similar changes to those seen in acute respiratory distress syndrome (ARDS), such as high-permeability edema, pulmonary vascular lesions, and eventual pulmonary fibrosis (Jones et al., 1984; Nash et al., 1967). When using HBO, oxygen is applied under increased pressure, therefore the systemic hyperoxic side effects are combined with side effects induced by the elevated pressure, such as barotrauma of the lungs and ears. Seizures with HBO have been reported with an incidence of 0.03% (Hampson and Atik, 2003), but these are self-limiting and cause no permanent damage (Clark and Lambertsen, 1971).

In addition to systemic side effects, hyperoxia is also associated with negative effects on brain tissue itself (Brucken et al., 2010; Oter et al., 2005). It is known to induce cerebral vasoconstriction in healthy individuals, leading to a decrease of CBF (Bulte et al., 2007). Exactly how NBO-induced vasoconstriction affects ischemic brain tissue is unclear, with results of several studies suggesting a possible beneficial effect. Shin and associates (2007) demonstrated an augmentation of CBF through NBO in ischemic brain tissue of rats subjected to a model of focal cerebral ischemia. In patients with severe TBI, Rangel-Castilla and colleagues (2010) found that hyperoxia-induced vasoconstriction led to an improved autoregulatory index, suggesting that this mechanism might allow cerebral vessels a better response to transient hypotension.

A further concern is the development of free oxygen radicals through hyperoxic treatment. Elevated levels of free oxygen radicals can cause loss of neurons and induce neurological deficits (Balentine, 1966; Mickel et al., 1990; Nakashima et al., 1999; Oh and Betz, 1991). In an experimental

Table 4. Results of Three Clinical Trials of Hyperbaric Oxygen Therapy (HBO) in Patients with Traumatic Brain Injury (TBI)

Study	n	HBO treatment	Time window (post-injury)	Results	Authors' conclusions	Comment
Artru et al., 1976	60	60 min daily for 10 days, repeated after a pause of 4 days	< 4.5 days	No differences were seen between HBO and controls in morbidity and mortality, apart from one subgroup (patients < 30 years of age with brainstem lesions)	No clear benefit from HBO treatment	High mortality rates in both groups, probably due to treatment modalities that have substantially changed today (e.g., forced hyperventilation)
Rockswold et al., 1992	168	60 min every 8 h for 2 weeks	6–24 h after admission	Reduced mortality in patients treated with HBO, no significant differences in functional outcome (GOS)	HBO reduces mortality in TBI; HBO treatment modalities (e.g., duration) have to be further investigated	Well-designed study; treatment modalities differ from today's standards (e.g., use of corticosteroids); relatively high overall mortality
Ren et al., 2001	55	40–60 min daily for 10 days, repeated after a pause of 4 days	< 24 h after admission	Improvement of neurological outcomes after 6 months (GOS) in HBO-treated patients; mortality rates not reported	HBO improves morbidity in patients with TBI and decreases elevated intracranial pressure	Major deficits in study design and documentation; differences in the study's treatment modalities and accepted guidelines (e.g., use of corticosteroids)

Three clinical trials of hyperbaric oxygen therapy (HBO) in patients with TBI have been carried out. The only study meeting today's standards for controlled prospective randomized trials was carried out by Rockswold and colleagues (1992). Patients had been enrolled from 1983–1989 in this study, so guidelines for the treatment of TBI patients have changed substantially since then.
GOS, Glasgow Outcome Scale.

model of global cerebral ischemia in gerbils, NBO of lasting 3 and 6 h resulted in high lipid peroxidation of brain tissue, and in a mortality rate three times higher than in non-treated animals (Mickel et al., 1987). In the hippocampi of rats subjected to experimental TBI (Ahn et al., 2008), 3-nitrotyrosine staining was elevated after a 1-h period of hyperoxic ventilation, demonstrating an oxidative damage to proteins. In contrast, other groups did not find any evidence of increased oxidative damage in experimental models of brain damage when hyperoxia was applied (Mink and Dutka, 1995; Schabitz et al., 2004; Singhal et al., 2002; Sunami et al., 2000).

In patients with TBI, Puccio and colleagues (2009) examined the effects of NBO for a period of 2 h on markers of oxidative stress, including lipid and protein peroxidation, antioxidant defenses, and glutathione. Analysis of these parameters in samples of patient cerebrospinal fluid (CSF) revealed no differences compared to samples from normoxic-treated patients. Rockswold and colleagues (2010) found no differences in levels of F2-isoprostane (a marker of oxidative damage) in CSF samples of TBI patients treated with NBO or HBO compared to controls.

As hyperoxic treatment seems to have beneficial as well as detrimental effects on brain tissue, positive effects may be diminished by negative effects. Finding the right balance is probably not based on an "all or nothing" principle; it is likely dependent on many factors, including therapeutic time window and dosage regimen. Further investigation is needed to identify pathophysiological mechanisms and optimum treatment modalities of therapeutic hyperoxia in order to evaluate the potential of this therapy and reduce its side effects. Threshold values have to be defined for hyperoxic treatment, since application of more oxygen than needed to have a neuroprotective effect would involve needless oxygen toxicity. Monitoring brain tissue oxygenation guides the clinician in avoiding hypoxia in cerebral tissue. It might also be a tool to identify excessive amounts of oxygen in brain tissue, so the term "brain oxygen tissue-directed therapy" would mean avoiding both hypoxia and detrimental hyperoxia.

Conclusion

The use of devices for monitoring brain tissue oxygenation allows identification of hypoxic episodes in brain tissue of TBI patients. Although controlled clinical trials have not yet been carried out, the available study results suggest that a brain tissue oxygen–directed therapy involving adjustments in therapeutic modalities to keep brain tissue oxygen levels above certain thresholds may improve mortality and functional outcomes in these patients. Additionally, the response of P_{BRO_2} to medical interventions such as increasing the inspired oxygen fraction might allow clinicians to draw important conclusions about the metabolic state of the patient's injured brain. Whether increasing oxygen in arterial blood to supraphysiological levels has a positive impact on cerebral metabolism and improves neurological outcomes remains unclear. The efficacy of hyperoxic treatment in TBI patients remains to be proven, and further studies as well as controlled and prospective clinical trials are needed. There are well-known side effects of hyperoxia, so neither implementation per guidelines nor the empiric use of increased oxygen in brain trauma victims is indicated at this time.

Author Disclosure Statement

No conflicting financial interests exist.

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