



# Multimodality Monitoring in Severe Traumatic Brain Injury

## *The Role of Brain Tissue Oxygenation Monitoring*

Jamin M. Mulvey,<sup>1\*</sup>, Nicholas W.C. Dorsch,<sup>2</sup> Yugan Mudaliar,<sup>1</sup> and Erhard W Lang,<sup>2</sup>

<sup>1</sup>Department of Intensive Care, University of Sydney, Westmead Hospital, Westmead Australia, and

<sup>2</sup>Department of Neurosurgery University of Sydney, Westmead Hospital, Westmead Australia

### Abstract

Traumatic brain injury (TBI) is a major cause of morbidity and mortality with widespread social, personal, and financial implications for those who survive. TBI is caused by four main events: motor vehicle accidents, sporting injuries, falls, and assaults. Similarly to international statistics, annual incidence reports for TBI in Australia are between 100 and 288 per 100,000. Regardless of the cause of TBI, molecular and cellular derangements occur that can lead to neuronal cell death. Axonal transport disruption, ionic disruption, reduced energy formation, glutamate excitotoxicity, and free radical formation all contribute to the complex pathophysiological process of TBI-related neuronal death. Targeted pharmacological therapy has not proved beneficial in improving patient outcome, and monitoring and maintenance of various physiological parameters is the mainstay of current therapy. Parameters monitored include arterial blood pressure, blood gases, intracranial pressure, cerebral perfusion pressure, cerebral blood flow, and brain tissue oxygenation. Currently, indirect brain oximetry is used for cerebral oxygenation determination, which provides some information regarding global oxygenation levels. Direct brain tissue oxygenation (ptiO<sub>2</sub>), a newly developed oximetry technique, has shown promising results for the early detection of cerebral ischaemia. ptiO<sub>2</sub> monitoring provides a safe, easy, and sensitive method of regional brain oximetry, providing a greater understanding of neurophysiological derangements and the potential for correcting abnormal oxygenation earlier, thus improving patient outcome. This article reviews the current status of bedside monitoring for patients with TBI and considers whether ptiO<sub>2</sub> has a role in the modern intensive care setting.

### \*Correspondence and reprint requests to:

Dr. Jamin Mulvey,  
JMO Management Unit,  
John Hunter Hospital,  
Locked Bag 1,  
Hunter Region Mail Centre,  
Newcastle, NSW, Australia  
2305.

E-mail: [jmulvey@ausdoctors.net](mailto:jmulvey@ausdoctors.net).



Humana Press

**Key Words:** Brain tissue partial pressure of oxygen; intracranial pressure; cerebral blood flow velocity; monitoring; severe head injury; cerebral ischaemia; transcranial Doppler ultrasound; Licox.

## Introduction

Injury to the brain causes significant morbidity and mortality through various mechanisms. Traumatic brain injury (TBI), regardless of the cause, has profound personal, social, and financial implications to those directly and indirectly involved. TBI can be classified as mild, moderate, or severe. Severe TBI, which is the main focus of this review, is clinically defined as any head injury that results in a postresuscitation Glasgow Coma Scale of 8 or less on admission or during the ensuing 48 hours (1). Studies of hospital admissions report that over 80% of TBI admissions are for mild-to-moderate injury, whereas severe TBI accounts for 5–15% (2–4). The overall mortality of patients with severe TBI who survive to reach hospital is between 25 and 65% (5–7).

Understanding the mechanisms of primary and secondary injury allows intensive care physicians and neurosurgeons to target therapy (8). Monitoring devices are used to detect disturbances of physiological parameters within the brain. Based on data obtained by multimodal monitoring devices, therapeutic measures may be used to correct abnormal values and potentially decrease patient morbidity and mortality. Because current neuroprotective pharmacotherapy has not proven beneficial (9–11), more emphasis is being placed on monitoring systemic and brain levels of physiological parameters as well as substrate availability (12–16). It is hypothesized that as monitoring devices improve and by maintaining substrate availability within the normal physiological range, the extent of secondary injuries will be reduced and patient outcome will improve.

The purpose of this article is to review the current status of bedside monitoring in the management of patients with TBI and evaluate the role of direct brain tissue oxygenation monitoring (ptiO<sub>2</sub>) in the intensive care setting.

Literature was identified through Medline and PubMed searches using the key words autoregulation, brain tissue oxygen tension pressure, cerebral blood flow velocity, cerebrovascular perfusion, Licox, severe head injury, and transcranial Doppler ultrasound (TCD). A reference library distributed by GMS (Kiel-Mielkendorf, Germany) and the senior author's library was also used for literature searches.

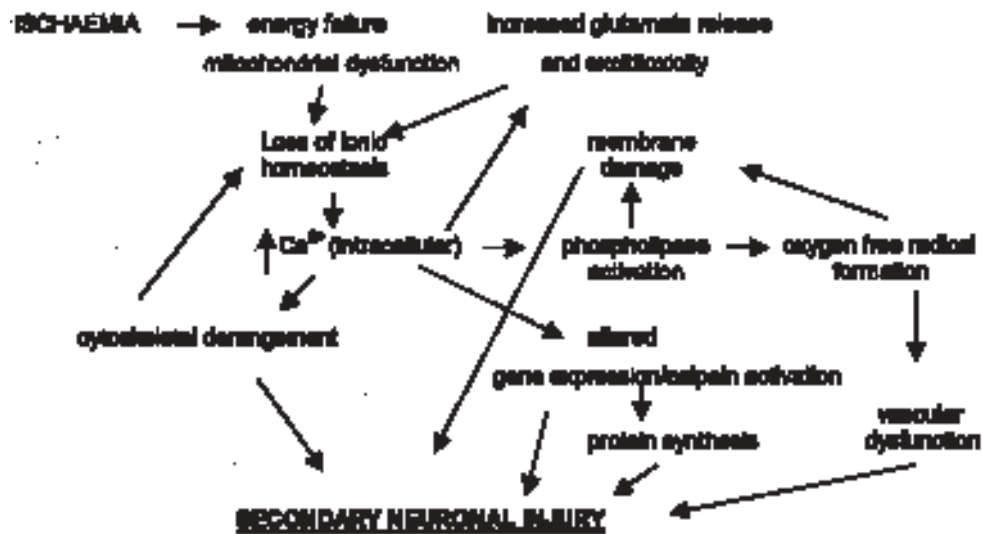
## Mechanisms of Cellular Injury: Primary and Secondary Injuries

Research over the past 20–30 years has elicited much information on the mechanisms leading to neuronal cell death. It has been shown that in both human and animal tissues, regardless of the precipitating factors (i.e., traumatic, ischaemic, hypoglycaemic), the basic mechanisms underlying neuronal degeneration and eventual death share similar cellular and molecular processes (see Fig. 1).

The processes that contribute to neuronal damage after injury can be classified into two main groups: the primary injury and the secondary injury (17–19). Direct brain injury, or the primary injury, results from both the direct impact to the brain and the changing forces involved from the sudden deceleration at the moment of impact. Large forces occur from acceleration, deceleration and rotation of the brain inside the cranium. Shearing forces occur between tissue planes of varying densities (20–22). This leads to immediate primary injury at the moment of trauma. The traumatic forces, as well as causing immediate structural damage to the neurons, cause secondary disruptions in membrane stability, intra-axonal cytoskeletal function, and axonal transport mechanisms (20). Data from experimental models of TBI have shown that postevent impairment of anterograde axoplasmic transport occurs, leading to local axonal swelling (23–25). With disorganization of microtubules and neurofilaments, continuation of this process leads to axonal disconnection, degradation, and distal degeneration.

Many aspects of the primary injury are immediate and irreversible, but it seems likely that a

Fig 1



**Fig. 1.** A schematic diagram representing the molecular events implicated in secondary neuronal injury caused by ischemia. Regardless of the pathological etiology, the sequences of events are intimately related and lead to neuronal death.

continuum exists between the primary injury and the development of the secondary injury (8). Although currently elusive, treatment aimed at avoiding the development of secondary injury, or even the earlier cessation of the progression of the primary injury, may influence the management and outcomes of TBI (10,11).

Secondary injury after insult is correlated to impaired cerebral metabolism, hypoxia, and ischemia, and a complex series of events ensue. Although a detailed outline of these processes are beyond the scope of this article, a brief synopsis of the mechanisms involved are presented, including mechanisms that may be clinically monitored in the intensive care unit (ICU).

### Cerebral Metabolism

Oxygen delivery is paramount to the normal metabolism of neurons. It is used in a variety of reactions within different cellular components to ultimately generate energy in the form of adenosine 5'-triphosphate (ATP) by aerobic glucose metabolism. Aerobic metabolism is the major source of energy formation in the brain, and neuronal survival relies on an adequate supply of oxygen and glucose by cerebral blood

flow. The aerobic metabolism of glucose includes the initial step of glycolysis, the tricarboxylic acid cycle, and the electron transport chain. Glucose is metabolized in the presence of oxygen to produce a higher ATP yield than occurs under hypoxic conditions. For an in-depth review of this topic, see ref. 26.

In an ischemic insult, loss of blood flow leads to decreased availability of oxygen and glucose. Anaerobic metabolism is a largely inefficient form of energy production, and as a result, rapid energy failure follows with decreased production of ATP (27). With decreasing levels of ATP, the physiological ionic homeostasis of the neuron is lost. Changes in the intracellular concentration of sodium, potassium, and calcium occur, leading to cellular injury and death. With progressive switching to anaerobic metabolism, lactate production rises sharply, as demonstrated by the lactate/pyruvate ratio (28–31). Increased lactate concentration and, therefore, tissue pH have been shown to correlate with a poor outcome in both animal and human models (28,32–35).

Cerebral metabolism can become severely deranged as a result of ischemic events, and

regional hypo- and hypermetabolism are known to occur (36). Depressed cerebral activity, mitochondrial dysfunction, and uncoupling of autoregulatory capacity of metabolic activity and substrate delivery have been strongly implicated (26,28,37,38).

### **Mitochondrial Dysfunction**

Mitochondria, which house the machinery for aerobic energy production, play an important role in aerobic metabolism. Mitochondrial dysfunction has been implicated in the impaired cerebral metabolism seen during ischemic episodes, including those resulting from TBI (39,40). Although not completely understood, the contribution of mitochondria to cerebral ischemic damage includes the impairment of ATP production, changes in mitochondrial permeability, and the release of factors that contribute to cell death (41). The most widely accepted hypothesis regarding mitochondrial dysfunction relates to the mitochondrial permeability transition (MPT) (42,43). MPT occurs as a result of the abnormal opening of protein channels between the inner and outer mitochondrial membrane secondary to ischemia. This results in mitochondrial swelling, membrane depolarization, loss of oxidative phosphorylation, and the release of proapoptotic proteins (44). The ischemic induction of mitochondrial dysfunction is a potential target for neuroprotective interventions and is currently the subject of extensive research.

### **Calcium-Induced Cellular Damage**

Loss of calcium homeostasis, with calcium entry into injured neurons, has long been associated with the process of delayed cell death (45,46). Calcium is physiologically important because it acts as a messenger to regulate the activity of lipolytic enzymes, proteolytic enzymes, protein kinases, protein phosphatases, and gene activation/expression. During insults such as ischemia or TBI, intracellular calcium increases uncontrollably and induces abnormal cellular machinery leading to neuronal death. Calcium antagonism has shown its utility as a neuroprotective agent in preclinical experi-

mental studies (47,48). This effect was not replicated in TBI clinical trials using the calcium channel blocker nimodipine, and there was no significant improvement in outcome (16,49,50).

### **Glutamate Excitotoxicity**

Excessive neuronal depolarization occurs during cerebral ischemia. Glutamate, an excitatory neurotransmitter, is released in larger quantities during cerebral ischemia than during normal physiological conditions and leads to opening of glutamate receptors and further activation of ion channels. Of particular significance is the sodium/calcium antiporter ion channel, which leads to an acute increase of both cations intracellularly (51). The *N*-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) glutamate receptors have been linked to the influx of calcium. The NMDA receptor directly opens a calcium channel, allowing a rapid influx of the calcium ion. The activated AMPA receptor opens a sodium channel allowing rapid influx of the sodium ion. Both ions, which are increased uncontrollably in ischemia, lead to the physiological derangements previously outlined. Increased intracellular calcium concentrations also stimulate glutamate release from presynaptic vesicles, further potentiating the pathological process (52). Although it would seem plausible that interventions targeting the glutamate excitotoxic cascade would improve outcomes in patients with TBI, clinical trials using the NMDA antagonist selfotel showed no significant improvement in the outcome of TBI (13,53–56).

### **Free Radical Formation**

Reperfusion injury caused by the production of free radicals has been theorized to contribute to secondary injury and delayed cell death. Oxygen free radicals are formed by the reperfusion-initiated metabolism of free fatty acids and arachidonic acid. The increased free radical formation leads to increased lipid peroxidation, protein oxidation, and DNA damage (57). The integrity of the cellular lipid membrane is compromised, which leads to failure of ionic

Au:  
Implicated  
in what? Pls  
clarify

partitioning and general cellular functioning, contributing to cell death. Clinical trials targeting the various pathological pathways described above have been investigated (58–63). Trials using pegorgotein, tirilazad, or triamcinolone have shown no significant improvement in overall morbidity or mortality in patients with TBI (14,64,65).

## The Utility of Combined Monitoring

### Overview

ICU management of TBI is aimed at preventing or reducing secondary injury. Following the poor results seen in pharmacotherapy clinical trials, current therapies focus on providing an environment in which the body's own cellular restorative processes are promoted. Systemic physiological parameters, including blood pressure, blood sugar level, electrolytes, and partial pressure of arterial dioxide (PaO<sub>2</sub>) and carbon dioxide (PaCO<sub>2</sub>) are monitored. In addition, specific cerebral parameters are equally important in neurologic intensive care.

The neurological monitoring modalities currently available can be classified into three types: pressure, flow, and oxygenation. Monitoring modalities include intracranial pressure (ICP) monitoring, TCD, and jugular venous oximetry (SjvO<sub>2</sub>). A new modality, which is still largely used as an experimental modality, is ptiO<sub>2</sub> (32,66,71). The physiological data gathered by using these monitoring modalities may allow greater understanding of the complex sequence of events that influence the final outcome in TBI. ICP and cerebral perfusion pressure (CPP) are the most important monitoring parameters on which therapeutic interventions are instituted. However, both reveal little in terms of cerebral oxygenation or cerebral blood flow.

### Invasive Cerebral Tissue Oxygen Monitoring

Currently available monitoring methods of cerebral oxygenation and cerebral blood flow detect a "global" measurement. The data obtained imply that the brain acts as a homogeneous structure; however, the heterogeneity of brain activity and substrate utilization is well-

known. With the high incidence of autoregulation dysfunction during TBI, global oxygenation measurements may be in the normal range and not reflect abnormal regional differences.

Probes can be used to measure regional values of brain tissue oxygen tension, carbon dioxide tension, and hydrogen ion concentrations (70,72–74). These multiparametric sensors are placed adjacent to the ICP monitoring catheter in the brain tissue via a modified skull bolt. Two types of commercially available ptiO<sub>2</sub> probes currently exist: Licox<sup>®</sup> and Neurotrend<sup>®</sup>. The Licox probe (GMS, Kiel-Mielkendorf, Germany) uses a polarographic cell in which oxygen diffuses from the tissue through a polyethylene wall of the catheter into its inner electrolyte chamber (Fig. 2A,B). Oxygen is transformed at the electrode, where it determines a current that reflects the tissue partial pressure of oxygen. The oxygen-sensitive sampling area of the polarographic gold cathode is approx 14 mm<sup>2</sup>.

The Neurotrend probe (Codman, Raynham, MA) uses optical sensors where dye, embedded in a plastic matrix, is connected to a fiberoptic cable. Depending on the gas concentration and pH of the surrounding tissues, the dye alters its properties, changing light transmission and reflecting tissue partial pressure of oxygen. The Neurotrend probe is comprised of four sensors and is able to measure ptiO<sub>2</sub>, ptiCO<sub>2</sub>, pH, and temperature. The sampling area of the Neurotrend probe is approximately 2 mm<sup>2</sup>.

ptiO<sub>2</sub> probes generally are placed in the right frontal lobe white matter in diffuse brain injury, or on the affected side in a hemispheric injury, and remain *in situ* for as long as ICP measurements are required (69,75). ptiO<sub>2</sub> probes are readily identified on computed tomography (CT) scanning (Fig. 3). This allows for correct placement and the accurate detection of oxygenation in either normal or pericontusional brain.

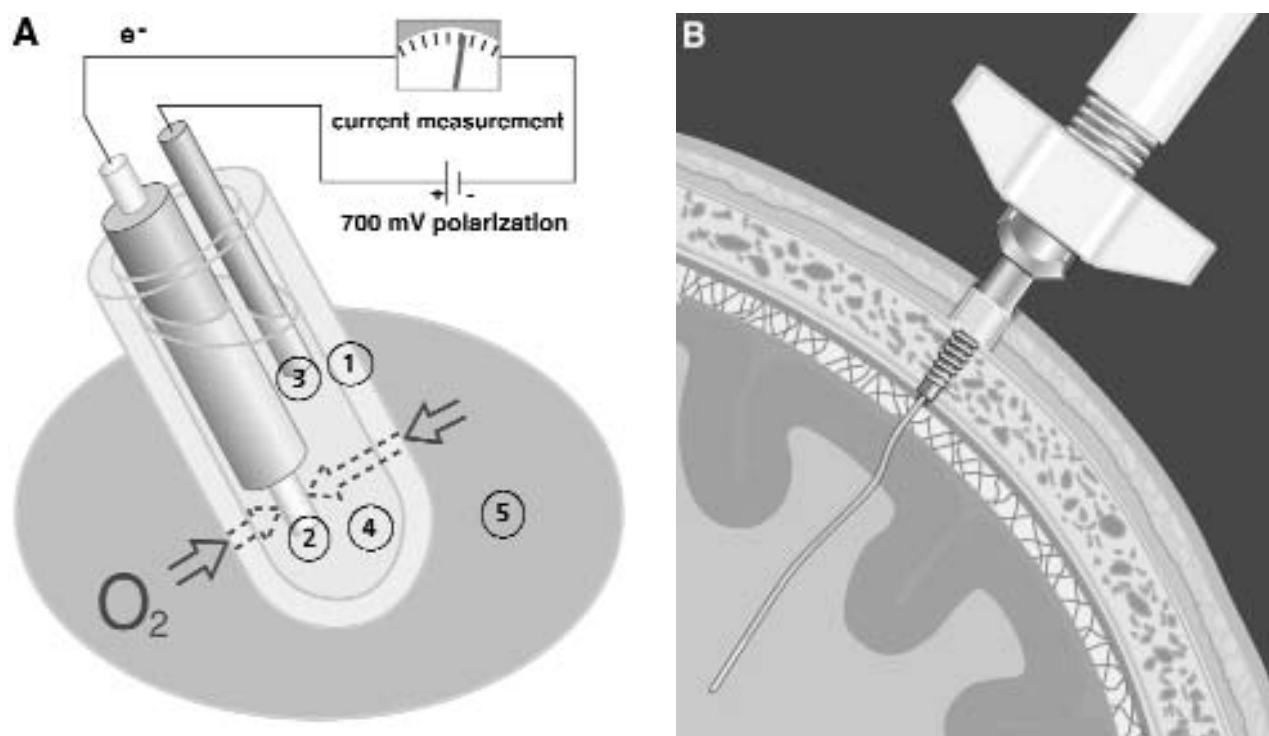
Normal values of ptiO<sub>2</sub> between 25 and 30 mmHg have been reported in experimental models (76). Studies have shown that in TBI, ptiO<sub>2</sub> values in patients with normal ICP and CPP are between 25 and 30 mmHg (77,78). The critical threshold for ischemic damage and a poorer outcome has been proposed at ptiO<sub>2</sub> val-

Fig 2

Au: Pls define ptiCO<sub>2</sub>

Fig 3

Au: Here you define ptiO<sub>2</sub> as direct brain tissue oximetry, but earlier as oxygenation...ok to use for both?



**Fig. 2. (A)** A schematic diagram of the Licox polarographic oxygenation probe. The numbered components of the diagram are: (1) polyethylene tube diffusion membrane; (2) polarographic gold cathode; (3) polarographic silver anode; (4) cell filled with electrolyte; and (5) cerebral tissue. **(B)** A schematic diagram of the Licox probe illustrating placement via a cranial bolt into the cerebral tissues. Placement is similar to ICP monitoring and is often used through the same bolt.

ues of 10–15 mmHg (69,77,79,81). Critical threshold is not the only factor that is important in terms of outcome; the duration spent below that threshold is important as well.

The metabolic heterogeneity of different tissue types is well-known. It is important to factor the heterogeneous nature of the brain when interpreting oximetry data. Experiments on rats have demonstrated the differing  $ptiO_2$  within the cortex depending on the depth of probe placement (82). It was proposed that the differing base levels related to the metabolism, microcirculation, and overall microstructure of each environment. Furthermore, depending on the probe's relationship to the arterial microvessels, a gradient within the tissues can exist with oxygen levels decreasing from artery to venous circulation. The microenvironment is influenced by the cerebral blood flow velocity of each

microenvironment, with low velocities showing the highest variability in terms of oxygenation differences (83). At times, the disparity between the different probe types can be appreciated, because sampling areas are quite different, and spatial heterogeneity must be compensated for by a sufficiently large sensor sampling area.

### Comparative Studies

#### $ptiO_2$ vs ICP/ CPP

Cerebral blood flow is physiologically regulated by several factors, including pressure of blood flow, the pressures within the cranial vault, and vascular autoregulatory processes. Following TBI, alterations in ICP and CPP are commonplace. A few studies have investigated the association between CPP, ICP, and  $ptiO_2$ . A prospective study of 23 patients with TBI inves-



**Fig. 3.** A computer tomography image demonstrating the position of a Licox oxygenation probe in the frontal cortex of a patient with TBI. Oxygenation probes are readily identifiable on scanning modalities, illustrating the position relative to contusional tissue and regions to be studied.

tigated the effects of aggressive treatment of CPP when below 60 mmHg. Dopamine infusion was always associated with an increase in  $ptiO_2$  (66). Intervention led to significant elevations of CPP from  $32 \pm 2$  to  $67 \pm 4$  mmHg and of  $ptiO_2$  from  $13 \pm 2$  to  $19 \pm 3$  mmHg. When initial CPP exceeded 60 mmHg, further CPP elevation did not significantly improve  $ptiO_2$ , suggesting a plateau phase of oxygenation. Another prospective study, comparing different methods of oxygenation monitoring in 17 patients with TBI showed that decreases in CPP below 60 mmHg were significantly correlated with decreases in  $ptiO_2$  (84). Furthermore, changes in  $SjvO_2$  were not significant when correlated with decreased CPP, and CPP values above 60 mmHg were not

associated with higher  $ptiO_2$ . This suggests that the critical threshold of CPP is 60 mmHg and that  $ptiO_2$  is more sensitive than  $SjvO_2$  to changes in CPP. In contrast, Hartl et al. (85) report that treatment of ICP with mannitol was not associated with improvements in  $ptiO_2$ . However, it should be noted that in this study, ICP was treated before it was severely raised ( $23 \pm 1$  mmHg), and initial CPP before treatment was  $68 \pm 2$  mmHg.

Focal ischemic tissue may at times have normal CPP but decreased  $ptiO_2$ . In a prospective study of nine patients who demonstrated acute focal lesions on CT scan and/or single photon emission computed tomography (SPECT) from either subarachnoid hemorrhage (SAH), TBI, or meningioma, changes in  $ptiO_2$  were investigated in relation to increased MAP and CPP (86).  $ptiO_2$  increased from  $24 \pm 13$  mmHg to  $31 \pm 13$  mmHg in a positive linear fashion when CPP increased from initial values of  $77 \pm 9$  mmHg to  $96 \pm 11$  mmHg ( $r^2 = 0.74$ ). However, in some patients with an initial  $ptiO_2$  below 20 mmHg, CPP was considered to be already within the normal range. These data suggest that although CPP values above 60 mmHg are usually associated with normal  $ptiO_2$ , CPP alone is not always accurate enough to assess brain tissue oxygenation.

ICP and CPP measurement and management form a major focus of current treatment in patients with TBI. Although severe alterations of ICP and CPP are correlated with poor outcome, studies suggest that other methods of monitoring would provide additional, and at times more sensitive, information regarding cerebral blood flow and substrate availability. Changes in  $ptiO_2$  are often detected concurrently with changes in CPP, but  $ptiO_2$  can be low (or even within the hypoxic range) even with normal values of CPP (86). A recent study has shown that in 18 of 26 patients after aneurysmal SAH or severe TBI who had a unilateral decompression hemicraniectomy for extensive cerebral oedema, pathological monitoring trends always preceded clinical deterioration (87). In 9 of 20 patients with SAH, decreases in  $ptiO_2$  occurred several hours before neurological deterioration

Au: Pls  
define MAP

or ICP increase. This was not always the case for patients with TBI. It is plausible that multimodal monitoring of ICP, CPP, and ptiO<sub>2</sub> could improve the sensitivity of detection of decreased cerebral blood flow and substrate availability. Therefore, early treatment interventions should increase the viability of injured and noninjured neuronal tissue, thereby improving patient outcome.

#### ptiO<sub>2</sub> vs CBF

Various investigators have studied the correlation between CBF and ptiO<sub>2</sub>, particularly in the initial periods of TBI when derangements in both CBF and ptiO<sub>2</sub> are often at their greatest. In considering these two clinical variables, it is important to remember that ptiO<sub>2</sub> reflects regional values, whereas CBF, depending on the modality used, may reflect either macro- or microcirculatory changes.

Doppenburg et al. investigated the correlations between CBF (Xenon computed tomography technique) and ptiO<sub>2</sub> in 25 patients with TBI and described a significant linear relationship between the two modalities ( $r = 0.74$ ,  $p = 0.0001$ ) (32). Patients with increased CBF showed higher ptiO<sub>2</sub>, whereas those with decreased CBF had a lower ptiO<sub>2</sub> below 26 mmHg. All patients in this study with ptiO<sub>2</sub> below 25 mmHg either died or remained vegetative.

Dings et al. investigated the relationship between ptiO<sub>2</sub>, CBF velocity (CBFV), and CO<sub>2</sub> reactivity in 17 patients with TBI (78). Low mean values for both ptiO<sub>2</sub> and CBFV were seen on the day of injury ( $7.7 \pm 2.6$  mmHg and  $60.5 \pm 32.0$  cm/second, respectively). Both variables increased, and by day 4 ptiO<sub>2</sub> was  $31.5 \pm 10.0$  mmHg and CBFV was  $87.9 \pm 21.0$  cm/second. The authors concluded that although ptiO<sub>2</sub> and CBFV increased simultaneously, CBFV increased further, suggesting vasospasm and uncoupling of flow and metabolism. To further support these findings, they discovered that at times during increased CBFV, both CPP and ptiO<sub>2</sub> were seen to decrease, indicating uncoupling or dysfunction of autoregulation. This suggests that ptiO<sub>2</sub> monitoring as an adjuvant

to CBF monitoring would provide increased accuracy in interpreting CBF values.

Although investigators have reported on the validity of cerebrovascular autoregulation assessment and its prognostic relationship to outcome, particularly related to CPP and CBFV, few have compared the correlation between these autoregulatory functions and ptiO<sub>2</sub> autoregulation (88–90). It appears that CBF/CBFV and ptiO<sub>2</sub> are generally correlated, but during autoregulatory dysfunction and uncoupling, monitoring of CBF/CBFV alone would at times provide misleading information regarding potential ischemic episodes. A recent publication by one of the present authors studying autoregulatory function of ptiO<sub>2</sub> in 14 patients with TBI, demonstrated a plateau phase for the CPP-ptiO<sub>2</sub> relationship similar to the autoregulatory plateau seen in the relationship between CPP and CBFV (71). When autoregulation was impaired, ptiO<sub>2</sub> increased in a linear fashion with increases in CPP. If autoregulation remained intact, then increases in CPP had minimal effect on ptiO<sub>2</sub>. It was concluded that manipulation of CPP was only of potential benefit in increasing brain oxygenation if autoregulatory mechanisms were dysfunctional. Furthermore, they suggested that continuous ptiO<sub>2</sub> monitoring would provide more sensitive information on the integrity of autoregulation after TBI, directing accurate therapy.

Cerebral oxygen reactivity/autoregulation has been assessed in patients with TBI by changing the fractional inspired oxygen concentration (FiO<sub>2</sub>) (33,91). The ability to increase ptiO<sub>2</sub> is particularly useful in conditions where normal autoregulatory function is impaired. By increasing FiO<sub>2</sub> from 35 to 100%, ptiO<sub>2</sub> is able to be increased to supranormal levels, allowing for aerobic metabolism. It has been proposed that FiO<sub>2</sub> manipulation can improve oxygenation better than CPP manipulation; however, patients with a high oxygen reactivity (indicating a significant disturbance in autoregulation) have a poorer outcome (69).

Au:Pls define CBF at first use. If meant for cerebral blood flow, define at first use with acronym in parentheses and use CBF throughout.

## ptiO<sub>2</sub> vs SjvO<sub>2</sub>

SjvO<sub>2</sub> monitoring has been widely used for global brain tissue oxygenation monitoring of patients with TBI since the early 1980s (92–94). Because ptiO<sub>2</sub> is an experimental modality, it is being used to detect ischemic episodes in patients with TBI (67,69,70,62,80,85). ptiO<sub>2</sub> measures direct regional oxygen tension levels, and investigators have compared the utility of ptiO<sub>2</sub> versus SjvO<sub>2</sub> in the detection of cerebral hypoxia/ischemic episodes.

In comparing these two methods of oximetry, it is important to consider (a) calibration, (b) the time of good-quality data (TGQD), and (c) complications.

### Calibration

The initial calibration of any monitoring device is crucial to obtaining accurate and reliable data. Based on the manufacturer's recommendations, ptiO<sub>2</sub> catheters are calibrated before insertion and after withdrawal from the brain tissue; no intramonitored calibration is possible. Two calibration parameters have been described for ptiO<sub>2</sub> catheters: sensitivity calibration and zero drift (68,70,77). Sensitivity calibration is defined as the difference in measured oxygen tension when room oxygen is measured, and zero drift is the difference in an oxygen-free solution. Calibration of SjvO<sub>2</sub> is based on co-oximetry readings, with comparisons made every 10–12 hours for the duration of its usage.

Licor ptiO<sub>2</sub> catheters have been shown to have minimal drift during continuous monitoring. In a prospective study of 15 patients with TBI comparing ptiO<sub>2</sub> and SjvO<sub>2</sub> monitoring, ptiO<sub>2</sub> monitoring showed low variability (3.7% sensitivity drift) and greater reliability over time (77). SjvO<sub>2</sub> monitoring required a total of 170 calibrations over 7 days, with 55% of calibrations showing an increased drift (>5%) when compared with co-oximetry. In a study by Dings et al. reporting on the stability and complications of ptiO<sub>2</sub> monitoring in 70 patients with either TBI or SAH, 54 Licor catheters showed a drift of  $-6.2 \pm 11.9\%$  (95). Sensitivity drift was greatest *in situ* during the first 4 days, after which

stability was improved. Gopinath et al. also reported low measured ptiO<sub>2</sub> values immediately after insertion; however, values usually stabilized within 60 minutes (67). van den Brink et al. reported low sensitivity drift ( $0 \pm 6\%$ ) and negligible zero drift in ptiO<sub>2</sub> (68). All authors concluded that Licor-based ptiO<sub>2</sub> measurement was a reliable method of detecting brain tissue ischemia over a prolonged period of time and that stability increased with time.

### The Time of Good, Quality Data

The efficiency and quality of information gathered by the different methods of oximetry can be quantified and compared. One method is through the function of TGQD, expressed by the equation: TGQD (%) =  $100 - [\text{time of artefacts (minute)} \times 100 / \text{total monitoring time (minute)}]$ .

In an investigation comparing ptiO<sub>2</sub> and SjvO<sub>2</sub> monitoring in 15 patients with TBI and altered CPP, TGQD and the total duration of monitoring differed greatly between the two oximetry methods (77). The median duration of monitoring reported was 9 days (range: 5–12) for ptiO<sub>2</sub> and 4 days (range: 3–7) for SjvO<sub>2</sub>. TGQD was reported at 95% (2491 hours total) and 43% (607 hours) for ptiO<sub>2</sub> and SjvO<sub>2</sub>, respectively. This difference in the SjvO<sub>2</sub> arm was attributed to poor light intensity in the system, repetitive calibrations, and dislocations. Meixensberger et al. reported similar disparities of TGQD between ptiO<sub>2</sub> and SjvO<sub>2</sub> monitoring (96). This prospective study of 45 patients with TBI reported TGQD for ptiO<sub>2</sub> and SjvO<sub>2</sub> at 95 and 40–50%, respectively. Only five patients were monitored with SjvO<sub>2</sub> for comparison because of increasing technical difficulties and poor reliability. Similar problems for SjvO<sub>2</sub> have been reported elsewhere (69).

Dings et al. have also studied the reliability of ptiO<sub>2</sub> (70). Investigating the technical and diagnostic reliability of ptiO<sub>2</sub> monitoring, 118 catheter probes were used in 101 patients with TBI. The TGQD was 99.2%, with artifacts related to transport, positioning of the patient, and displacement of the catheter or the bolt. Dings

et al. concluded that ptiO<sub>2</sub> was a safe and reliable technique for monitoring cerebral oxygenation.

However, not all studies have found ptiO<sub>2</sub> to be superior to SjvO<sub>2</sub> in the detection of critical ischemic episodes. A prospective study comparing the utility of the methods in 65 patients with TBI concluded that both modalities should be used in conjunction and that neither identifies all episodes of cerebral ischemia (67). Of 65 patients, 7 were unable to have ptiO<sub>2</sub> data collected because of technical difficulties. Of those monitored, no significant difference was found in the TGQD, with values of 90 and 88% for SjvO<sub>2</sub> and ptiO<sub>2</sub> monitoring, respectively ( $p = 0.524$ ). Decreases in oxygenation were detected simultaneously in 90% of episodes; however, only 66% of these episodes saw both modalities below critical thresholds.

### Complications

Oximetry is an invasive procedure and carries a potential for complications related to insertion and continuous monitoring. For routine ICU purposes, probes are inserted via single or multiple lumen bolts if other monitoring modalities are combined. Depending on the hospital's policies, bolts can be inserted in the ICU. In operative cases, probes can be inserted directly during surgery.

In studies to date, complication rates for both ptiO<sub>2</sub> and SjvO<sub>2</sub> are low. Numerous studies using ptiO<sub>2</sub> have reported complication rates below 3% (67,70,95). These complications involved secondary hematoma formation, none of which required treatment. The insertion trauma can cause microhemorrhages and an edema zone around the probe tract (97). This has minimal effect on measurements and does not compromise accuracy. Complications were related to technical issues such as the accidental removal of the catheter during transport, broken catheter cables, or unidentified technical problems. These technical problems were reduced with experience, and larger studies have reported zero complication rates for the insertion of ptiO<sub>2</sub> catheters (68,69).

The technique of ptiO<sub>2</sub> probe placement is almost identical to ICP monitor placement. Thus, it seems plausible that ptiO<sub>2</sub> probe could be inserted by practitioners other than neurosurgeons. A retrospective study looking at the complication rates of ICP probe insertion by neurosurgeons, general surgical registrars, and intensivists found no significant difference in complication rates between the different groups (98). They concluded that the use of non-neurosurgeons for the placement of probes could provide the prompt and early monitoring of high-risk patients. We propose that it would be safe practice to utilize non-neurosurgeons for ptiO<sub>2</sub> probe insertion; however, a neurosurgeon should be on standby if complications occur.

Complication rates for SjvO<sub>2</sub> monitoring are similarly low. Gopinath et al. reported zero complications related to SjvO<sub>2</sub> monitoring in 58 patients (67). Kiening et al. reported dislodgement as a main complication but did not quantify the rate (77). In a prospective study of 44 patients admitted to ICU for TBI, SAH, or stroke and requiring SjvO<sub>2</sub> monitoring, complication rates were below 5% and were clinically insignificant (99).

### Brain Oxygenation and Outcome

No randomized control trials have been conducted to demonstrate improved outcome with one monitoring modality over another. ICP monitoring has become routine practice in the neuro-ICU worldwide, although it has never been subjected to randomized controlled trials. Uncontrolled intracranial hypertension is negatively correlated with outcome (100–102). It also seems plausible that reduced brain oxygenation would be correlated with a poorer outcome.

Regardless of the lack of controlled trial data, current clinical trials investigating the utility of ptiO<sub>2</sub> suggest that prolonged periods of hypoxia correlate with a poor outcome. van Santbrink et al. studied the utility of ptiO<sub>2</sub> in 22 patients with TBI and showed that hypoxic periods in the acute posttraumatic phase was common (69). More than 80% of patients showed prolonged

hypoxic periods less than 20 mmHg in the first 24 hours postinjury. In five patients,  $ptiO_2$  fell below 5 mmHg within the first 24 hours, and four of those were either dead or partial vegetative state at 6 months. In the patients who had monitoring within the acute phase without a  $ptiO_2$  drop below 5 mmHg, 15 had good outcome measures, and only 1 died or was vegetative at 6 months.  $ptiO_2$  was found to be strongly correlated to outcome.

Kiening et al. have also demonstrated poor outcome with reduced brain oxygenation in TBI (66). In 16 patients followed for 6 months postinjury, the number of ischemic episodes was associated with outcome. An ischemic episode was defined as a  $ptiO_2$  less than 10mmHg for longer than 15 minutes. In the first week postinjury, the numbers of ischemic episodes were always associated with a poorer outcome on the Glasgow Outcome Scale (GOS). Interestingly, absence of episodic hypoxia did not ensure a favorable outcome. Bardt et al. also demonstrated poor outcome with prolonged ischemic episodes (81). In 35 patients with TBI, analysis of data showed significant differences in outcome measures when  $ptiO_2$  was less than 10mmHg for more than 30 minutes. In patients with less than 30 minutes of hypoxia during the monitoring period, GOS analysis at discharge demonstrated that 80% were either vegetative or severely disabled, 20% had a favorable outcome, and no patients died acutely. In this same group, GOS at 6 months showed that 72.8% had a favorable outcome, 18.2% were vegetative or severely disabled, and 9% died. In contrast, in patients with more than 30 minutes of hypoxia, 48% died acutely and 52% had an unfavorable GOS at discharge. In those discharged, GOS at 6 months showed that 55.6% had died, 22.2% were severely disabled, and 22.2% had a favorable outcome. Bardt et al. concluded that even short periods of hypoxia adversely affected outcome and that functional recovery is possible in the prolonged hypoxia arm at 6 months.

## Conclusions

TBI is a major cause of morbidity and mortality worldwide. Although management has

improved significantly over the past 30 years, mortality is still alarmingly high in those who survive to hospital. Because the pharmacological management of TBI is currently poor and still under extensive research, the integration and management of physiological variables remain the mainstay of current therapy.

$ptiO_2$  monitoring has received widespread attention and has generated regular international meetings. Although it has become a routine monitoring tool in several neurosurgical and neurological ICUs, it is still considered experimental in other centers. Based on the data available, it has been shown to provide a safe, easy-to-use, and accurate method of cerebral oximetry determination. It can provide additional, sensitive information regarding brain oxygen availability, autoregulation, and brain perfusion in patients with TBI. Compared to other oximetry methods,  $ptiO_2$  has minimal complications, increased accuracy, and greater *in situ* monitoring time.  $ptiO_2$  often provides more sensitive information than current monitoring methods regarding regional CBF, CPP, ICP, and oxygen availability. Indeed, some current therapeutic interventions used to manipulate ICP/ CPP and thought to improve oxygenation may, in fact, cause hypoxia. Brain tissue oxygenation monitoring has the potential to detect early ischemic injury before alterations in other variables occur and may improve patient outcome.

## References

1. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81–84.
2. Hillier SL, Hiller JE, Metzger J. Epidemiology of traumatic brain injury in South Australia. *Brain Inj* 1997;11:649–659.
3. Jennett B. Epidemiology of head injury. *J Neurol Neurosurg Psychiatry* 1996;60:362–369.
4. Sorensen SB, Kraus JF. Occurrence, severity and outcomes of brain injury. *J Head Trauma Rehab* 1991;6:1–10.
5. Murray GD, Teasdale GM, Braakman R, et al. The European Brain Injury Consortium survey of head injuries. *Acta Neurochir* 1999;141:223–236.

Au: For all references, please list at least first 6 authors, but et al. after three if there are more than 6.

6. Lang EW, Pitts LH, Damron SL, Rutledge R. Outcome after severe head injury: an analysis of prediction based upon comparison of neural network versus logistic regression analysis. *Neurol Res* 1997;19:274–280.
7. Marshall L, Gautille T, Klauber M, et al. The outcome of severe closed head injury. *J Neurosurg* 1991; 75:S28-S36.
8. Reilly PL. Brain injury: the pathophysiology of the first hours. 'Talk and die revisited'. *J Clin Neurosci* 2001;8:398–403.
9. Faden AI. Neuroprotection and traumatic brain injury: the search continues. *Arch Neurol* 2001; 58:1553–1555.
10. Clausen T, Bullock R. Medical treatment and neuroprotection in traumatic brain injury. *Curr Pharm Des* 2001;7:1517–1532.
11. Maas AI. Neuroprotective agents in traumatic brain injury. *Expert Opin Investig Drugs* 2001; 10:753–767.
12. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *J Neurotrauma* 2002; 19:503–557.
13. Morris GF, Bullock R, Marshall SB, Marmarou A, Maas AIR, Marshall LF. 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.
14. Marshall LF, Maas A, Marshall S, et al. A multi-centre trial on the efficacy of using tirilazad mesylate in cases of head injury. *J Neurosurg* 1998; 89:519–525.
15. Miller JD, Marshall LF. Are steroids useful in the treatment of head-injured patients? *Surg Neurol* 1996;45:296.
16. Maas AI, Steyerberg EW, Murray GD, et al. Why have recent trials of neuroprotective agents in head injury failed to show convincing efficacy? A pragmatic analysis and theoretical considerations. *Neurosurgery* 1999;44:1286–1298.
17. Graham DI, Adams JH, Doyle D. Ischaemic brain damage in fatal non-missile head injuries. *J Neurol Sci* 1978;39:213–234.
18. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993;34:216–222.
19. Chesnut RM. Secondary brain insults after head injury: clinical perspectives. *New Horiz* 1995 ;3:366–375.
20. Povlishock JT, Christman CW. The pathobiology of traumatically induced axonal injury in animals and humans: a review of current thoughts. *J Neurotrauma* 1995;12:555–564.
21. Jennett B, Teasdale G. Structural Pathology. In: Jennett B, Teasdale G, eds. *Management of Head Injuries*. Vol. 20. Philadelphia: F.A. Davis Company, 1981:19–43.
22. Maxwell WL, Watt C, Graham DI, Gennarelli TA. Ultrastructural evidence of axonal shearing as a result of lateral acceleration of the head in non-human primates. *Acta Neuropathol (Berl)* 1993;86:136–144.
23. Erb DE, Povlishock JT. Axonal damage in severe traumatic brain injury: an experimental study in cat. *Acta Neuropathol* 1988;76:347–358.
24. Maxwell WL, Irvine A, Graham DI, et al. Focal axonal injury: the early axonal response to stretch. *J Neurocytol* 1991;20:157–164.
25. Povlishock JT, Becker DP, Cheng CLY, Vaughan GW. Axonal change in minor head injury. *J Neuropath Exp Neurol* 1983;42:225–242.
26. Zauner A, Daugherty WP, Bullock MR, Warner DS. Brain oxygenation and energy metabolism: Part I-biological function and pathophysiology. *Neurosurgery* 2002;51:289–302.
27. Siesjo BK. Cerebral circulation and metabolism. *J Neurosurg* 1984;60:883–908.
28. Zauner A, Clausen T, Alves OL, et al. Cerebral metabolism after fluid-percussion injury and hypoxia in a feline model. *J Neurosurg* 2002;97:643–649.
29. Valadka AB, Goodman JC, Gopinath SP, Uzura M, Robertson CS. Comparison of brain tissue oxygen tension to microdialysis-based measures of cerebral ischemia in fatally head-injured humans. *J Neurotrauma* 1998;15:509–519.
30. Rehn Crona S, Rosen I, Siesjo BK. Brain lactic acidosis and ischemic cell damage. I. Biochemistry and neurophysiology. *J Cereb Blood Flow Metab* 1981;1:297–311.
31. Pulsinelli WA, Levy D, Duffy TE. Regional cerebral blood flow and glucose metabolism following transient forebrain ischemia. *Ann Neurol* 1982;11:499–509.
32. Dopperberg EMR, Zauner A, Bullock MR, Ward JD, Fatouros PP, Young HF. Correlations between brain tissue oxygen tension, carbon dioxide, pH, and cerebral blood flow—a better way of monitoring the severely injured brain? *Surg Neurol* 1998;49:650–654.

33. Menzel M, Doppenberg E, Zauner A, Soukup J, Reinert M, Bullock R. 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.
34. Menzel M, Doppenberg EM, Zauner A, et al. Cerebral oxygenation in patients after severe head injury: monitoring and effects of arterial hyperoxia on cerebral blood flow, metabolism and intracranial pressure. *J Neurosurg Anesthesiol* 1999;11:240-251.
35. Voldby B, Enevoldsen EM, Jensen FT. Cerebrovascular reactivity in patients with ruptured intracranial aneurysms. *J Neurosurg* 1985;62:59-67.
36. Ritter AM, Robertson CS. Cerebral metabolism. *Neurosurg Clin N Am* 1994;5:633-645.
37. Sutton RL, Hovda DA, Adelson PD, Benzel EC, Becker DP. Metabolic changes following cortical contusion: relationship to edema and morphological changes. *Acta Neurochir (suppl)* 1994; 60:446-448.
38. Mulvey JM, Renshaw GMC. Brainstem neuronal oxidative hypometabolism in response to hypoxic pre-conditioning in the epaulette shark (*Hemiscyllium ocellatum*). *Neurosci Lett* 2000 ;290:1-4.
39. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF. Cerebral circulation and metabolism in severe traumatic brain injury: the elusive role of ischemia. *J Neurosurg* 1991;75:685-693.
40. Xiong Y, Peterson PL, Lee CP. Alterations in cerebral energy metabolism induced by traumatic brain injury. *Neurol Res* 2001;23:129-138.
41. Sims NR, Anderson MF. Mitochondrial contributions to tissue damage in stroke. *Neurochem Int* 2002;40:511-526.
42. Crompton M. The mitochondrial permeability transition pore and its role in cell death. *Biochem J* 1999;341:233-249.
43. Blomgren K, Zhu C, Hallin U, Hagberg H. Mitochondria and ischemic reperfusion damage in the adult and in the developing brain. *Biochem Biophys Res Com* 2003;304:551-559.
44. Neumar RW. Molecular mechanisms of ischemic neuronal injury. *Ann Emerg Med* 2000;36: 483-506.
45. Goldberg MP, Choi DW. Combined oxygen and glucose deprivation in cortical cell culture: calcium-dependent and calcium-independent mechanisms of neuronal injury. *J Neurosci* 1993; 13:3510-3524.
46. Siesjo BK, Bengtsson F. Calcium fluxes, calcium antagonists, and calcium-related pathology in brain ischemia, and spreading depression: a unifying hypothesis. *J Cereb Blood Flow Metab* 1989; 9:127-140.
47. Kazda S, Garthoff B, Krause HP, Schlossmann K. Cerebrovascular effects of the calcium antagonistic dihydropyridine derivative nimodipine in animal experiments. *Arzneimittelforschung* 1982;32:331-338.
48. Archer DP, Pappius HM. Effects of two dihydropyridine calcium channel blockers on cerebral metabolism and blood flow in traumatized rat brain. *Neurochem Pathol* 1986;5:117-130.
49. Teasdale G, Bailey I, Bell A, et al. A randomized trial of nimodipine in severe head injury: HIT I. British/Finnish Co-operative Head Injury Trial Group. *J Neurotrauma* 1992;9:S545-S550.
50. Harders A, Kakarieka A, Braakman R. Traumatic subarachnoid hemorrhage and its treatment with nimodipine. German tSAH study group. *J Neurosurg* 1996;85:82-89.
51. Choi DW. Ionic dependence of glutamate neurotoxicity. *J Neurosci* 1987;7:369-379.
52. White BC, Sullivan JM, DeGracia DJ, et al. Brain ischemia and reperfusion: molecular mechanisms of neuronal injury. *J Neurol Sci* 2000; 179:1-33.
53. McCulloch J, Ozyurt E, Park CK, Nehls DG, Teasdale GM, Graham DI. Glutamate receptor antagonists in experimental focal cerebral ischaemia. *Acta Neurochir Suppl (Wien)* 1993; 57:73-79.
54. Park CK, Nehls DG, Graham DI, Teasdale GM, McCulloch J. Focal cerebral ischaemia in the cat: treatment with the glutamate antagonist MK-801 after induction of ischaemia. *J Cereb Blood Flow Metab* 1988;8:757-762.
55. Panter SS, Faden AI. Pretreatment with NMDA antagonists limits release of excitatory amino acids following traumatic brain injury. *Neurosci Lett* 1992;136:165-168.
56. Tsuchida E, Rice M, Bullock R. The neuroprotective effect of the forebrain-selective NMDA antagonist CP101,606 upon focal ischemic brain damage caused by acute subdural hematoma in the rat. *J Neurotrauma* 1997;14:409-417.
57. Siesjo BK. Basic mechanisms of traumatic brain damage. *Ann Emerg Med* 1993;22:959-969.
58. Smith SL, Andrus PK, Gleason DD, Hall ED. Infant rat model of the shaken baby syndrome: preliminary characterization and evidence for the role of free radicals in cortical hemorrhaging

- and progressive neuronal degeneration. *J Neurotrauma* 1998;15:693-705.
59. Clark WM, Hazel JS, Coull BM. Lazaroids. CNS pharmacology and current research. *Drugs* 1995;50:971-983.
  60. Wienkers LC, Steenwyk RC, Mizesak SA, Pearson PG. In vitro metabolism of tirilazad mesylate in male and female rats. Contribution of cytochrome P450C11 and delta 4-5 alpha-reductase. *Drug Metab Dispos* 1995;23:383-392.
  61. Smith SL, Andrus PK, Zhang JR, Hall ED. Direct measurement of hydroxyl radicals, lipid peroxidation, and blood-brain barrier disruption following unilateral cortical impact head injury in the rat. *J Neurotrauma* 1994;11:393-404.
  62. Hall ED, Andrus PK, Yonkers PA. Brain hydroxyl radical generation in acute experimental head injury. *J Neurochem* 1993;60:588-594.
  63. Sanada T, Nakamura T, Nishimura MC, Isayama K, Pitts LH. Effect of U74006F on neurologic function and brain edema after fluid percussion injury in rats. *J Neurotrauma* 1993;10:65-71.
  64. Grumme T, Baethmann A, Kolodziejczyk D, et al. Treatment of patients with severe head injury by triamcinolone: a prospective, controlled multicenter clinical trial of 396 cases. *Res Exp Med (Berl)* 1995;195:217-229.
  65. Young B, Runge JW, Harrington T, et al. Effects of pegorgotein on neurologic outcome of patients with severe head injury. A multicenter, randomized controlled trial. *JAMA* 1996;276:538-543.
  66. Kiening KL, Hartl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR. Brain tissue pO<sub>2</sub> monitoring in comatose patients: implications for therapy. *J Neurol Res* 1997;19:233-240.
  67. Gopinath SP, Valadka AB, Uzura M, Robertson CS. Comparison of jugular venous oxygen saturation and brain tissue pO<sub>2</sub> as monitors of cerebral ischemia after head injury. *Crit Care Med* 1999;27:2337-2345.
  68. van den Brink WA, van Santbrink H, Steyerberg WW, et al. Brain oxygen tension in severe head injury. *Neurosurgery* 2000;46:868-878.
  69. van Santbrink H, Maas A, Avezaat C. Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. *Neurosurgery* 1996;38:21-31.
  70. Dings J, Meixensberger J, Jager A, Roosen K. Clinical experience with 118 brain tissue oxygen partial pressure catheter probes. *Neurosurgery* 1998;43:1082-1094.
  71. Lang EW, Czosnyka M, Mehdorn HM. Tissue oxygen reactivity and cerebral autoregulation after severe traumatic brain injury. *Crit Care Med* 2003;31:267-271.
  72. Gupta AK, Hutchinson P, Al-Rawi P, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. *Anesthesia and Analgesia* 1999;88:549-553.
  73. Zauner A, Bullock R, Di X, Young HF. Brain oxygen, CO<sub>2</sub>, pH and temperature monitoring: evaluation in the feline brain. *Neurosurgery* 1995;37:1168-1177.
  74. Zauner A, Doppenberg EMR, Woodward JJ. Multiparametric continuous monitoring of brain metabolism and substrate delivery in neurosurgical patients. *Neurol Res* 1997;19:265-273.
  75. Meixensberger J, Baunach S, Amschler J, Dings J, Roosen K. Influence of body position on tissue-pO<sub>2</sub>, cerebral perfusion pressure and intracranial pressure in patients with acute brain injury. *Neurol Res* 1997;19:249-253.
  76. Maas AIR, Fleckenstein W, de Jong DA. Monitoring cerebral oxygenation: experimental studies and preliminary clinical results of continuous monitoring of cerebrospinal fluid and brain tissue oxygen tension. *Acta Neurochir* 1993;59(suppl):50-57.
  77. Kiening KL, Unterberg AW, Bardt TF, Schneider GH, Lanksch WR. Monitoring of cerebral oxygenation in patients with severe head injuries: brain tissue pO<sub>2</sub> versus jugular vein oxygen saturation. *J Neurosurg* 1996;85:751-757.
  78. Dings J, Meixensberger J, Amschler J, Hamelbeck B, Roosen K. Brain tissue pO<sub>2</sub> in relation to cerebral perfusion pressure, TCD-findings and TCD-CO<sub>2</sub> reactivity after severe head injury. *Acta Neurochir* 1996;138:425-434.
  79. Dings J, Jager A, Meixensberger J, Roosen K. Brain tissue pO<sub>2</sub> after severe head injury. *Neurol Res* 1998;20(suppl):71-75.
  80. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue pO<sub>2</sub> to outcome after severe head injury. *Crit Care Med* 1998;26:1576-1581.
  81. Bardt TF, Unterberg AW, Hartl R, Kiening KL, Scheider GH, Lanksch WR. Monitoring of brain tissue pO<sub>2</sub> in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta Neurochir Suppl* 1998;71:153-156.

82. Baumgartl H, Lubbers DW. Microcoaxial needle sensors for polarographic measurements of local  $O_2$  in the cellular range of living tissue. In: Gnaiger E, Forstner H, eds. *Polarographic Oxygen Sensors*. New York: Springer Verlag, 1983:37–65.
83. Lubbers DW, Baumgartl H. Heterogeneities and profiles of oxygen pressure in brain and kidney as examples of  $pO_2$  distribution in the living tissue. *Kidney International* 1997;51:372–380.
84. Sarrafzadeh AS, Unterberg AW, Keining KL, Bardt T, Schneider GH, Lanksch WR. Monitoring of cerebral oxygenation in traumatic brain injured patients. In: Bauer BL, Kuhn TJ, eds. *Severe Head Injuries*. Berlin: Springer Verlag, 1997:109–120.
85. Hartl R, Bardt T, Keining KL, Sarrafzadeh AS, Schneider GH, Unterberg AW. Mannitol decreases ICP but does not improve brain tissue  $pO_2$  in severely head-injured patients with intracranial hypertension. *Acta Neurochir* 1997;70(suppl):40–42.
86. Stocchetti N, Chierigato A, De Marchi M, Croci M, Benti R, Grimoldi N. High cerebral perfusion pressure improves low values of local brain tissue  $O_2$  tension ( $ptiO_2$ ) in focal lesions. *Acta Neurochir* 1998; 71(suppl):162–165.
87. Strege RJ, Lang EW, Stark AM, et al. Cerebral edema leading to decompressive craniectomy: An assessment of the preceding clinical and neuromonitoring trends. *Neurol Res* 2003:accepted.
88. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 1996;27:1829–1834.
89. Bouma G, Muizelaar J. Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. *J Neurotrauma* 1992;9:S333–S348.
90. Lang E, Mehdorn H, Dorsch N, Czosnyka M. Continuous monitoring of cerebrovascular autoregulation: a validation study. *J Neurol Neuros Psychiatry* 2002;72:583–586.
91. Fandino J, Stocker R, Prokop S, Imhof HG. Correlation between jugular bulb oxygen saturation and partial pressure of brain tissue oxygen during  $CO_2$  and  $O_2$  reactivity tests in severely head-injured patients. *Acta Neurochir (Wien)* 1999;141:825–834.
92. Robertson CS, Narayan RK, Contant CF, et al. Clinical experience with a continuous monitor of intracranial compliance. *J Neurosurg* 1989;71:673–680.
93. Cruz J, Miner ME, Allen SJ, Alves WM, T.A. G. Continuous monitoring of cerebral oxygenation in acute brain injury: assessment of cerebral hemodynamic reserve. *Neurosurgery* 1991;29:743–749.
94. Cruz J, Raps EC, Hoffstad OJ, Jaggi JL, Gennarelli TA. Cerebral oxygenation monitoring. *Crit Care Med* 1993;21:1242–1246.
95. Dings J, Meixensberger J, Roosen K. Brain tissue  $pO_2$  monitoring: catheter stability and complications. *Neurol Res* 1997;19:241–245.
96. Meixensberger J, Jager A, Dings J, Baunach S, Roosen K. Quality and therapeutic advances in multimodality neuromonitoring following head injury. In: Bauer BL, Kuhn TJ, eds. *Severe Head Injuries*. Berlin: Springer Verlag, 1997:109–120.
97. van den Brink WA, Haitzma IK, Avezaat CJ, Houtsmuller AB, Kros JM, Maas AI. Brain parenchyma/ $pO_2$  catheter interface: a histopathological study in the rat. *J Neurotrauma* 1998;15:813–824.
98. Kaups KL, Parks SN, Morris CL. Intracranial pressure monitor placement by midlevel practitioners. *J Trauma* 1998;45:884–886.
99. Coplin WM, O'Keefe GE, Grady MS, et al. Thrombotic, infectious, and procedural complications of the jugular bulb catheter in the intensive care unit. *Neurosurg* 1997;41:101–109.
100. Lang EW, Chesnut RM. Intracranial pressure. Monitoring and management. *Neurosurg Clin N Am* 1994;5:573–605.
101. Narayan RK, Kishore PR, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. *J Neurosurg* 1992;56:650–659.
102. Zink BJ. Traumatic brain injury outcome: concepts for emergency care. *Ann Emerg Med* 2001;37:318–332.

Au: Ref  
87:Pls  
update

Table 1  
Brain Oxygenation Studies

Author	No. of Patients	Diagnosis	Modality	Duration of Monitoring	Conclusions
Doppenburg (32)	25	TBI CBF	ptiO <sub>2</sub>	Unreported	ptiO <sub>2</sub> correlated with CBF Measures true substrate delivery and represents regional CBF
Kiening (66)	23	n = 21 TBI n = 2 cerebral hematoma	ptiO <sub>2</sub> ICP CPP	1-12 d	ptiO <sub>2</sub> < 18 mmHg had 100% mortality ptiO <sub>2</sub> below 10 mmHg for longer than 10 min was always associated with a poor outcome Increasing CPP increased ptiO <sub>2</sub> Decreasing ICP doesn't significantly improve ptiO <sub>2</sub> Hyperventilation normalizes ICP/ CPP but can reduce ptiO <sub>2</sub> Complications related to ptiO <sub>2</sub> resulting from inexperience No infectious complications TGQD was 90% vs 88% (SjvO <sub>2</sub> vs ptiO <sub>2</sub> ) Neither modalities detected all ischemic episodes Both modalities would compliment each other, particularly if ptiO <sub>2</sub> was placed in an ischemic but salvageable part of the brain
Gopinath (67)	58	TBI	ptiO <sub>2</sub> SjvO <sub>2</sub> ICP CPP	90.6 h	
van Santbrink (69)	22	TBI	ptiO <sub>2</sub> SjvO <sub>2</sub> ICP CPP	74.3 h ptiO <sub>2</sub> (4.0-113.5 h) 97.0 h SjvO <sub>2</sub> (15.8-144)	Similar duration of monitoring between ptiO <sub>2</sub> and SjvO <sub>2</sub> ; however, 80% of calibrations in SjvO <sub>2</sub> were inaccurate Low sensitivity drift for ptiO <sub>2</sub> Poor correlation between ptiO <sub>2</sub> and SjvO <sub>2</sub> Poor correlation between ptiO <sub>2</sub> and ICP, and CPP Hyperventilation for ICP treatment decreased ptiO <sub>2</sub> in some patients
Dings (70)	101	n = 57 TBI n = 43 SAH n = 1 brain tumor	ptiO <sub>2</sub> ICP CPP	6.7 ± 3.9 d	Hematoma formation rate from ptiO <sub>2</sub> 1.7% Technical complication rate 13.6% Probe adaptation time approx 60 min TGQD 99.2%
Lang (71)	14	TBI	ptiO <sub>2</sub> CPP ICP CBFV	1-15 days <sup>a</sup>	ptiO <sub>2</sub> increased with CPP increase during autoregulation dysfunction If autoregulation was intact, CPP manipulation wouldn't change ptiO <sub>2</sub>
Kiening (77)	15	TBI	ptiO <sub>2</sub> SjvO <sub>2</sub> CPP	ptiO <sub>2</sub> 9 d (5-12 d) SjvO <sub>2</sub> 4 d (3-7 d)	ptiO <sub>2</sub> could be performed for twice the duration of SjvO <sub>2</sub> TGQD for ptiO <sub>2</sub> and SjvO <sub>2</sub> was 95% and 43%, respectively 55% of calibrations for SjvO <sub>2</sub> showed greater than 5% drift CPP >60 mmHg did not improve oxygenation ptiO <sub>2</sub> more suitable for long term oxygenation monitoring

Dings (78) for greater than 30 min always associated	17	TBI	ptiO <sub>2</sub>	1–12 d <sup>a</sup>	ptiO <sub>2</sub> below 10mmHg TCD	with a poor outcome
Bardt (81)	35	TBI	CPP CBFV ptiO <sub>2</sub> ICP CPP	119.3 ± 65.7 h 8.6 d (2.5–12)	Cerebral hypoxia correlated with increase ICP and low CPP Incidence of frequent episodes of hypoxia associated with a poor outcome at discharge and 6 mo, including death ptiO <sub>2</sub> has 95.2% TGQD SjvO <sub>2</sub> has TGQD 66.4% ptiO <sub>2</sub> decreased with all CPP decreases <60 mmHg Significant correlation between ptiO <sub>2</sub> and CPP <60 mmHg When ICP >20 mmHg, mannitol infusion significantly changed ICP and CPP	
Sarrafzadeh (84)	17	TBI		Unclear		
Hartl (85)	11	TBI				
Dings (95)	70	SAH or TBI <sup>b</sup>	ptiO <sub>2</sub> ICP CPP	7.5 ± 4.0 d	No significant change was detected with ptiO <sub>2</sub> or SjvO <sub>2</sub> Drift greatest in the first 4 d (ptiO <sub>2</sub> ) No infections related to catheter insertion 2.7% hematoma formation related to catheter insertion	
Meixensberger (96)	45	TBI	ptiO <sub>2</sub> SjvO <sub>2</sub> SNM	7.5 ± 3.4 d	2.7% hematoma formation with ptiO <sub>2</sub> TGQD was 95 and 40–50% (ptiO <sub>2</sub> and SjvO <sub>2</sub> , respectively) Critical low thresholds seen in 50% cases on day 1 posttrauma Hyperventilation treatment for ICP control in patients with a critical ptiO <sub>2</sub> worsened tissue ischemia Mannitol recommended first line treatment for patients with low ptiO <sub>2</sub> and raised ICP	

TBI, ; CBF, ; ICP, ; CPP, ; ptiO<sub>2</sub>, ; SjvO<sub>2</sub>, ; TGQD, ; SAH, ; DBFV, ; SNM, .

Au: Pls provide footnotes for a and b

Au: Pls spell out all acronyms in Table footnote

Table 2  
Clinical Diagnoses Where Direct Brain  
Oxygenation Monitoring May be Clinically  
Beneficial

---

*Clinical Condition*

---

Traumatic brain injury  
Subarachnoid hemorrhage  
Stroke  
Tumor

---