Parenchymal Brain Oxygen Monitoring in the Neurocritical Care Unit

Peter D. Le Roux, MD[a,*], Mauro Oddo, MD[b]

KEYWORDS

• Brain monitoring • Brain oxygen • Clark electrode • Hypoxia • Neurocritical care
• Optical fluorescence • Traumatic brain injury • Subarachnoid hemorrhage

KEY POINTS

- Parenchymal brain tissue oxygen ($PbtO_2$) monitoring is a safe and reliable technique for continuous bedside evaluation of patients with severe brain injury.
- Two techniques, a modified Clark electrode that uses the electrochemical properties of noble metals or optical fluorescence technology, can be used to measure $PbtO_2$.
- $PbtO_2$ indicates the balance between regional oxygen supply and cellular oxygen consumption and may be described by the equation $PbtO_2 = CBF \times AVTo_2$, where CBF is cerebral blood flow, Pvo_2 is partial oxygen pressure in mixed venous blood, and $AVTo_2$ is $Pao_2 - Pvo_2$.
- $PbtO_2$ values less than 20 mm Hg are considered worth treating and values less than 15 mm Hg are consistent with brain hypoxia or ischemia.
- Reduced $PbtO_2$ is associated with worse outcome in acute brain injury in adults and children, although the strength of this relationship may depend on probe location.
- When severe traumatic brain injury care is based on data from both a $PbtO_2$ and intracranial pressure (ICP) monitor, some (but not all) observational series suggest that outcome is better than when just ICP-based care is provided.

INTRODUCTION

Patients with a variety of severe, acute neurologic disorders such as traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), acute ischemic stroke, and intracerebral hemorrhage (ICH) often are admitted to the neurocritical care unit (NCCU). Despite much research and success in animal models, effective drug therapies for these disorders have not been identified in clinical trials.[1] Instead, much of patient management in the NCCU is centered on the early identification and removal of mass lesions and on the detection, prevention, and management of secondary brain insults that exacerbate outcome (eg, hypotension, hypoxia, seizures, increased intracranial pressure [ICP]). Careful and repeated assessment and monitoring of clinical and laboratory findings, imaging studies, and bedside physiologic data are consequently what drive modern neurocritical care.

A variety of monitors are currently in clinical use (**Box 1**), although the ideal monitor to assess neurologic function in the NCCU does not yet exist. These monitors may be classified into 2 broad categories: (1) radiographic or tomographic techniques that provide information at a single point in time, and (2) bedside monitors that may

[a] The Brain and Spine Center, Lankenau Medical Center, 100 E. Lancaster Ave, Wynnewood, PA 19096, USA;
[b] Service de Médecine Intensive Adulte, Medico-Surgical ICU, Centre Hospitalier Universitaire Vaudois - CHUV, Rue du Bugnon 46, Lausanne 1011, Switzerland
* Corresponding author.
E-mail address: lerouxp@mlhs.org

Neurosurg Clin N Am 24 (2013) 427–439
http://dx.doi.org/10.1016/j.nec.2013.03.001
1042-3680/13/$ – see front matter

Box 1
Examples of monitors in clinical use in the NCCU

- Clinical evaluation, serial assessment
- Laboratory analysis
- Systemic: electrocardiogram, heart rate, blood pressure, O_2 saturation, end tidal CO_2 (Et_{CO_2}), temperature
- Hydraulic: ICP/cerebral perfusion pressure (CPP)
- Electrophysiology: electroencephalogram, somatosensory evoked potentials, brain stem auditory evoked response
- Radiographic/tomographic: positron emission tomography (PET), single-photon emission computed tomography, CT-P, stable Xe-CT (^{133}XE), magnetic resonance imaging (MRI)
- Cerebral blood flow (CBF): transcranial Doppler, laser Doppler, thermal diffusion probe, transcranial cerebral oximetry
- Metabolic: microdialysis, jugular venous oximetry, direct brain oxygen, near infrared spectroscopy
- Biosamples (cerebrospinal fluid or serum): eg, S100B, GFAP, NSE

Abbreviations: CT-P, CT – perfusion scan (computed tomography); GFAP, Glial fibrillary acidic protein; NSE, neuron specific enolase.

be subdivided into monitors that are (1) invasive or noninvasive, or (2) continuous or noncontinuous. More than 1 monitor is ideally used because the brain is a complex organ and no single method can provide complete information about its health. Furthermore, monitoring by itself does not alter outcome. Instead, it is how the information provided by the monitor is used that contributes to patient wellbeing, particularly when targeted to patient-specific pathophysiology. This article reviews one type of continuous physiologic monitor: direct measurement of parenchymal brain oxygen.

THE IMPORTANCE OF BRAIN OXYGEN

Maintenance of adequate tissue oxygenation is a fundamental objective in critical care medicine in general, and the assessment of tissue oxygenation is indispensable to care of the critically ill patient. The adult brain represents about 2% of body weight, but consumes about 20% of the oxygen consumed by the body. Greater than 90% of this oxygen is used by the mitochondria to produce ATP, which is integral to cell function.[2] For this energy metabolism, brain cells must be supplied with oxygen and glucose, the primary fuel for the brain (although, in some circumstances, lactate also may be used).[3] Only then, and with normal mitochondrial function, can sufficient energy (ATP) be produced to maintain neuronal integrity and function. The brain lacks fuel stores and requires a continuous supply of glucose and oxygen. Therefore, continuous CBF, cerebral oxygen tension and delivery, and normal mitochondrial function are of vital importance to maintain brain function and tissue viability.

DEFINITION

There are 4 basic methods to measure brain oxygen: jugular venous bulb oximetry, direct brain tissue (parenchymal) oxygen tension measurement, near infrared spectroscopy, and oxygen-15 PET. This article discusses parenchymal brain oxygen measurement, the commonest technique currently used in the NCCU to assess cerebral oxygenation. Brain tissue oxygen, or parenchymal brain oxygen, is defined as the partial pressure of oxygen in the brain interstitial space and reflects the availability of oxygen for oxidative energy production. There has been debate about whether the technique measures tissue oxygen pressure or tension, and, accordingly, several abbreviations have been used for brain tissue oxygen. A consensus conference at the 13th International Symposium on Intracranial Pressure and Brain Monitoring held in July 2007 in San Francisco, California, proposed that $PbtO_2$ be used as the standard abbreviation. Hence, this article uses $PbtO_2$ when referring to brain tissue oxygen or parenchymal brain oxygen. Consistent with this abbreviation, recent clinical studies suggest that $PbtO_2$ may be best defined by the equation: $PbtO_2 = CBF \times AVT_{O_2}$, where AVT_{O_2} is $Pa_{O_2} - Pv_{O_2}$ (ie, $PbtO_2$ represents the interaction between plasma oxygen tension and CBF).[4]

TECHNOLOGY

Brain oxygen ($PbtO_2$) monitors were first used in the clinical environment in 1993 and included in the treatment guidelines for severe TBI in 2007.[5] Two techniques are available: (1) a modified Clark electrode that uses the electrochemical properties of noble metals (eg, Licox, Integra Lifesciences, Plainsboro, NJ; or Neurovent-P Temp, Raumedic AG, Munchberg, Germany), and (2) optical fluorescence technology (eg, Neurotrend, Diametrics Medical, St Paul, MN, and Codman, Johnson & Johnson, Raynham, MA; and OxyLab P_{O_2}, Oxford Optronix Ltd, Oxford, UK).

The Licox probe has been most frequently used in the NCCU. It is based on the Clark principle, which is a temperature-dependent oxygen-consuming process, and so a temperature probe is supplied with the $PbtO_2$ probe. This temperature probe measures brain temperature and allows for automatic calibration. The new Licox PMO probe can measure $PbtO_2$ and brain temperature using a single probe.[6] The Clark principle uses the electrochemical properties of noble metals to measure tissue oxygen content.[7] The Clark electrode consists of a membrane that covers a layer of electrolyte and 2 metallic electrodes. Oxygen diffuses through the membrane and is electrochemically reduced at the cathode. The greater the oxygen partial pressure, the more oxygen diffuses through the membrane. The change in voltage between the reference electrode and the measuring electrode is proportional to the amount of oxygen being reduced on the cathode. The Neurovent-P Temp, which uses the same polagraphic technique as the Licox, can also measure $PbtO_2$ and brain temperature with 1 catheter. There are important differences in values obtained by the Neurovent and Licox, and so the values obtained by these devices cannot be used interchangeably.[8,9] The Licox system averages oxygen over a probe area of 14 to 18 mm^2 and has excellent long-term stability, even after 7 days. The Neurovent-P Temp has a greater surface area (24 mm^2).

The second technique used to measure $PbtO_2$ is based on fluorescence quenching in which a marker changes color according to the ambient amount of gas. Optode sensors are used to measure concentrations of substances by photochemical reactions that create changes in indicator compound optical properties.[7] Unlike the Licox, this process does not consume oxygen and does not affect the measured oxygen level. However, the probe measures a smaller area. The Neurotrend uses this technique but it is no longer commercially available for clinical use. The accuracy and clinical stability of the Neurotrend sensor also seems to be less than the Licox system.[10] There are several other important differences between the Clark principle (eg, the Licox) and optical techniques (eg, Neurotrend). First, Licox catheters are precalibrated and so can be inserted without any preuse calibration. However postinsertion stabilization (about 1 hour) is required before readings are reliable. By contrast, the Neurotrend monitor needs bedside calibration to a defined oxygen concentration. Second, the catheters are of different lengths; the Neurotrend is inserted at a greater depth than the Licox catheter. Third, the critical $PbtO_2$ threshold for hypoxia is different and so it is difficult to compare studies that use the different techniques. In addition, the Neurotrend changed design in 1998, making it difficult to compare between old and more recent studies that describe this technology.[11]

Direct $PbtO_2$ monitors provide a measure of $PbtO_2$ in units of tension (mm Hg). A conversion factor of 1 mm Hg = 0.003 mL O_2/100 g brain can be used to convert $PbtO_2$ values to units of concentration (mL O_2/100 cm^3). A $PbtO_2$ monitor is not a blood flow monitor. Instead, it indicates the balance between regional oxygen supply and cellular oxygen consumption and may be described by the equation: $PbtO_2 = CBF \times AVTo_2$ (ie, the interaction between plasma oxygen tension and CBF).[4] $PbtO_2$ is influenced by many factors (**Box 2**), including CBF and the factors that regulate it, such as CO_2 and mean arterial blood pressure (MAP) but also with changes in arterial oxygen tension (Pao_2) and so lung function and hemoglobin.[11–14] In addition, a $PbtO_2$ monitor is different from a jugular bulb catheter that measures the venous oxygen content in blood leaving the brain (ie, the balance between oxygen delivery and oxygen use). By contrast, $PbtO_2$ is consistent with the oxygen that accumulates in brain tissue and PET studies suggest it may correlate inversely with the oxygen extraction fraction[15] and reflect oxygen diffusion rather than total oxygen delivery or metabolism.[14,16,17]

MONITOR INSERTION

Parenchymal brain oxygen measurement involves the insertion of a fine catheter (about 0.5 mm in

Box 2
Factors that may influence brain oxygen

- Local factors of major influence on $PbtO_2$
  - Oxygen consumption of neurons and glia cells
  - Oxygen diffusion conditions/gradients in tissue
  - Number of perfused capillaries per tissue volume
  - Length and diameter of perfused capillaries
  - Capillary perfusion rate and microflow pattern
  - Hemoglobin oxygen release in microcirculation
- Systemic factors of major influence on $PbtO_2$
  - Arterial BP, ICP, Pao_2, $Paco_2$, pH, temperature
  - Blood hemoglobin content, P50, viscosity, and hematocrit

diameter) into the brain tissue, specifically the white matter. The $PbtO_2$ catheters or probes can be inserted through a single-lumen or multiple-lumen bolt secured in a burr hole or they may be tunneled under the scalp. The procedure to insert the monitor may be performed in the operating room or at the bedside in the NCCU. $PbtO_2$ monitors usually are placed by neurosurgeons but, in some institutions, neurointensivists may insert these devices with neurosurgical backup. In general, $PbtO_2$ monitors are placed for similar reasons as an ICP monitor (ie, Glasgow Coma Scale [GCS] $\leq$8). The Licox system includes a brain temperature probe (thermocouple) that is inserted through a triple-lumen bolt with the $PbtO_2$ and ICP monitor (eg, Camino, Integra Neuroscience). However, if brain temperature is not measured (eg, a microdialysis catheter is inserted through the lumen instead of the temperature probe), the monitor should be calibrated manually on a regular basis (eg, every 30 minutes) by using core body temperature. Hemorrhage is the most common procedural complication and is identified in less than 1% of parenchymal monitors. Most of these are identified on imaging and are not of clinical importance. An INR less than or equal to 1.6 and platelet count of more than 100,000 are necessary to safely place an ICP or $PbtO_2$ monitor. Infection is rare[18] but device malfunction, similar to other monitors, may require troubleshooting in up to 10% of devices.

NORMAL AND ABNORMAL $PBTO_2$ VALUES

Physiologic studies suggest that mitochondria need an oxygen concentration of 1.5 mm Hg to produce ATP.[19] This level corresponds with a $PbtO_2$ between 15 and 20 mm Hg. A similar $PbtO_2$ level is observed using 7-T MRI techniques and fluorescent quenching techniques. $PbtO_2$ threshold values depend on what type of monitor is used. In general, when using a Licox monitor, $PbtO_2$ greater than 2–30 mm Hg is considered normal; these values have been verified in awake patients undergoing elective functional neurosurgical procedures.[20,21] $PbtO_2$ values less than 20 mm Hg are considered worth treating and values less than 15 mm Hg are consistent with brain hypoxia or ischemia (**Table 1**).[11,21–24,48,49]

REGIONAL VERSUS GLOBAL MEASUREMENT

$PbtO_2$ probes sample approximately 15 mm^2 of tissue around the tip and the $PbtO_2$ value depends on oxygen diffusion from the vasculature to a small amount of tissue.[4,16] Therefore, it is a regional monitor, whose values depend on probe location (**Fig. 1**), which has led to debate about probe location and whether the value can be used to make decisions about global oxygenation. In most patients, $PbtO_2$ is measured in normal-appearing (ie, on admission computed tomography [CT] scan) frontal subcortical white matter; there is evidence that this local measurement is an indicator of global oxygenation.[11,22,25,26,42,43] Consistent with this, 2 clinical studies have shown good correlation between $PbtO_2$ and jugular bulb venous oxygen saturation (Sjo_2), used to assess global brain oxygenation, in areas without focal disorders after TBI.[22,25] In areas with focal disorders, this correlation between $PbtO_2$ and Sjo_2 was absent and the $PbtO_2$ values reflected regional brain oxygenation better than jugular bulb oximetry.[25] Other studies also show that, when the probe is in tissue immediately adjacent to a contusion or other disorder (eg, a subdural hematoma), values are often lower, even if CPP is higher.[27,50,51] In addition, when the monitor is placed adjacent to abnormal brain, regional hypoxia lasts longer than in normal-appearing tissue[50] and the relationship with outcome seems to be more robust.[27]

Table 1
Licox $PbtO_2$ values

Condition	$PbtO_2$ Values (mm Hg)
Increased	>50[a]
Normal	25–35
Compromised; begin treating	20[b]
Brain hypoxia	15
Severe brain hypoxia	10
Cell death	<5

[a] The meaning of supranormal $PbtO_2$ values is unclear.
[b] In a National Institutes of Health–sponsored phase II trial currently underway to study $PbtO_2$, treatment is initiated when $PbtO_2$ is less than 20 mm Hg. Other investigators suggest treatment be initiated when $PbtO_2$ is less than 15 mm Hg.
Data from Refs.[11,15,20,22–47]

PRACTICAL USE IN THE NCCU

Once inserted, a run-in or equilibration time of up to 1 hour is required before readings are stable. Adjustment of insertion depth (when used through an access device) is not possible with the Licox system and, if the monitor is removed, the insertion bolt then should be replaced if a new monitor is inserted to avoid potential contamination. The position and function of the $PbtO_2$ monitor should ideally be confirmed with a head CT scan or oxygen challenge test, particularly if the initial $PbtO_2$ reading after 30 to 60 minutes of stabilization is

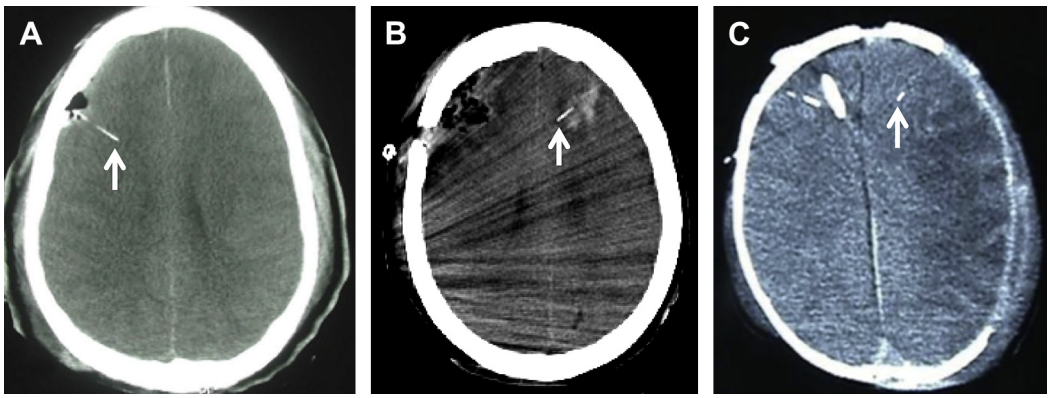

Fig. 1. A computed tomography (CT) head scan shows a Licox $PbtO_2$ probe (*arrow*) in (*A*) what appears to be normal white matter of the right frontal cortex, (*B*) in a contusion, and (*C*) adjacent to the penumbra. Brain oxygen levels may vary because of position. In particular, the probe in the contusion is unlikely to respond to an oxygen challenge and so would be considered nonfunctional.

abnormal. Transiently increasing the fraction of inspired oxygen (Fio_2) and observing the corresponding $PbtO_2$ increase can help confirm function or exclude the presence of surrounding microhemorrhages or sensor damage at insertion. An oxygen challenge is therefore performed when monitoring starts and, in some institutions, daily thereafter as part of regular clinical care to evaluate the function and responsiveness of the $PbtO_2$ probe or to determine oxygen reactivity. The oxygen challenge involves increasing the Fio_2 from baseline to 1.0 for approximately 5 minutes. This increase typically leads to a several-fold increase in the amount of oxygen dissolved in the plasma, translating into a mean 3-fold increase in $PbtO_2$.[4,13,14] However, the response to hyperoxia usually is less robust when the monitor is in an underperfused (CBF <20 mL/100 g/min) region.[52]

There are no specific recommendations on how long $PbtO_2$ should be monitored. In patients with TBI, we leave the monitor in place until ICP is normal for 24 hours without any specific treatment other than sedation for ventilation. On average, in patients with severe TBI this is 4 to 5 days. In patients with SAH, we tend to keep the monitor in place during the risk period for vasospasm. In addition, continuous $PbtO_2$ can be monitored twice as long as Sjo_2 and without needing recalibration. In studies that compare $PbtO_2$ with Sjo_2, good-quality data are acquired 95% of the time with $PbtO_2$, but only 43% of the time for Sjo_2.[22] Postinsertion noncontrast head CT confirmation of probe position in the brain parenchyma is important to interpret readings.[17,27,50] In some patients, a CT-perfusion study also may be useful. For example, if $PbtO_2$ readings are consistently low or poorly responsive to therapy, it is useful to know the monitor's proximity to a focal abnormality or whether the region it is in is hypoperfused. In these cases, the $PbtO_2$ threshold for treatment may be lower than normally used.

THE PHYSIOLOGIC RATIONALE BEHIND $PBTO_2$ MONITORING

Monitoring in the NCCU has traditionally focused on ICP and its control. There is a large body of literature that shows a relationship between increased ICP, including even short episodes, and mortality.[53,54] The relationship between ICP and outcome among survivors is less clear[55] and, although ICP treatment benefits some patients, the results in large clinical series are less certain.[56–59] In part, this may stem from trial design, center variation, and prognostic heterogeneity. In addition, current management is largely a reactive model in which an abnormal value (threshold) from a single parameter triggers corrective action(s) to reverse the process largely in a phenomenological rather than mechanistic manner. Hence treatment of the acutely injured brain based on an individual parameter (eg, ICP and CPP) may be an oversimplified approach to patient care,[60–63] and further treatment advances may depend on more rather than less information to better target and individualize care.

Several lines of clinical evidence using a variety of techniques suggest that $PbtO_2$ monitors, among other tools, may be an ideal complement to ICP monitors and hence targeted management of select patients in the NCCU. First, in cerebral microdialysis studies, decreases in $PbtO_2$ are associated with markers of cellular dysfunction[64]; hence $PbtO_2$ monitoring may be useful in clinical conditions in which cerebral ischemia or secondary brain injury may occur.[15] Second, pericontusional brain

tissue exhibits persistent increase of lactate/pyruvate ratio (ie, cell energy dysfunction) independently of CPP.[65] Third, metabolic changes in the brain may occur before ICP increases.[66,67] Fourth, studies using jugular bulb catheters or $PbtO_2$ monitors show evidence for cellular hypoxia in the brain despite normal ICP and CPP in both adults and children, and that these events are common.[28–31,68–71] Fifth, PET studies show that cellular hypoxia after TBI is associated with abnormal oxygen diffusion rather than a perfusion deficit.[16] Together these findings suggest that a $PbtO_2$ monitor may provide unique, more, or earlier information about pathophysiologic changes occurring in the brain after acute injury that can supplement or complement information from other devices. An alternative is that $PbtO_2$ may be considered a novel target for resuscitation following brain injury and so expand potential therapeutic options.[31]

CLINICAL USE IN THE NCCU

A large body of observational clinical $PbtO_2$ data, primarily in patients with severe TBI and, less frequently, in SAH, has accrued since the early 1990s. In addition, use of $PbtO_2$ monitors has been described in several other conditions including brain tumors, intracerebral hemorrhage, stroke, cerebral edema associated with metabolic abnormalities, and meningitis. Recommendations about use are derived mainly from retrospective case-control and prospective observational studies. Based on these studies, $PbtO_2$ monitoring is recommended in patients with a GCS less than 9, particularly when there is an abnormal head CT scan or the patient is at risk for delayed ischemia (ie, when ICP monitoring is indicated).

$PbtO_2$ monitoring is best used with other monitors (eg, an ICP monitor) and, like all other monitors, the information provided by a $PbtO_2$ monitor should be interpreted with data from the clinical examination, other monitors, and CT scan findings. The pathophysiologic changes that occur in the brain after injury, in the broad sense, are complex and different pathophysiologic processes may occur simultaneously or sequentially, and to varying degrees. Hence, use of a $PbtO_2$ and ICP (or other) monitor(s) together can improve insight about this complex pathophysiology (eg, provide information about autoregulation or help identify an optimal CPP target), and so allow intensive care unit staff to design strategies of care that are individualized and targeted.[72,73] Consistent with this, observational data suggest that $PbtO_2$ monitoring can potentially guide (eg, identify) potential deleterious effects of treatment or define responders and nonresponders of several therapies, including (1) CPP[15,74–76]; (2) induced hypertension[74,77]; (3) osmotherapy and hypertonic saline use[78,79]; (4) decompressive craniectomy DC[80–82]; (5) hyperventilation[12,83–85]; (6) normobaric hyperoxia, although its role in resuscitation remains controversial[86–88]; (7) blood transfusion, particularly in patients with impaired cerebrovascular reserve who may be better transfused when oxygen delivery is compromised rather than a hemoglobin threshold reached[32,89–94]; (8) fluid balance[95]; (9) titration of sedatives, including use of propofol or barbiturates for burst suppression or ICP control[96–98]; (10) induced normothermia[99,100]; (11) ventilator control[101,102]; or (12) define optimal body position for nursing a patient.[103] Furthermore, information from a $PbtO_2$ monitor may help define a subset of patients who are at risk for patient transport.[104] In patients with SAH, $PbtO_2$ has also been used to help detect delayed cerebral ischemia (DCI) and to evaluate the effects of various therapies for DCI, angiography, or pharmacologic angioplasty.[74,105–107] In addition, studies in SAH have shown that, in some patients, nimodipine or intra-arterial papaverine can have unexpected adverse effects on $PbtO_2$.[108,109]

Use During Neurosurgical Procedures

$PbtO_2$ monitor use during neurosurgical procedures, in particular aneurysm or arteriovenous malformation (AVM) surgery is well described.[106,110,111] A correctly positioned $PbtO_2$ monitor allows the effects of temporary arterial occlusion to be examined; reduced $PbtO_2$ and especially brain hypoxia indicate low CBF and are associated with cerebral infarction.[110] $PbtO_2$ measurements have also been used during surgery to examine oxygenation of cerebral tissue during AVM or tumor surgery.[111,112] Reduced $PbtO_2$, before AVM resection suggests low perfusion and chronic hypoxia, whereas a marked $PbtO_2$ increase after AVM removal indicates hyperperfusion. The effects of inhalational agents[113] and propofol[98] on cerebral autoregulation and oxygenation during anesthesia have been examined using $PbtO_2$ monitoring. These studies show a dose-dependent loss of autoregulation but a corresponding increase in $PbtO_2$ provided CPP is maintained with inhalational agents, but not with propofol.

BRAIN OXYGEN INDICES

$PbtO_2$ Reactivity

The increase in $PbtO_2$ relative to an increase in arterial P_{O2} is termed brain tissue oxygen reactivity. It is thought that this reactivity is controlled by an oxygen regulatory mechanism, and that this mechanism may be disturbed after brain

injury. Van Santbrink and colleagues[114] examined the brain tissue oxygen response (ie, the change in $PbtO_2$ in response to changes in Pao_2) and showed that a greater response in the first 24 hours after injury was independently associated with an unfavorable outcome. The effect of $Paco_2$ on this mechanism has been studied in dogs[115] and in pigs[12]: $PbtO_2$ shows a linear correlation with CO_2 and MAP. A linear correlation with CBF during CO_2 reactivity testing was also found, which suggest that $PbtO_2$ is influenced by factors that regulate CBF, namely CO_2 and MAP.

Oxygen Reactivity Index

Soehle and colleagues[116] introduced the concept of $PbtO_2$ autoregulation, defined as the ability of the brain to maintain $PbtO_2$ despite CPP changes. This concept may facilitate identification of appropriate individual CPP targets. Additional studies by Lang and colleagues[73] showed a significant correlation between static cerebral autoregulation (determined using blood flow velocity in relation to changing CPP) and cerebral tissue oxygen reactivity (the rate of $PbtO_2$ change relative to changing CPP).[117] This finding suggests a close link between regulation of CBF and oxygenation. Impaired brain tissue oxygen pressure reactivity index is associated with worse outcome after TBI,[72] SAH,[118,119] and stroke.[72] These findings suggest that manipulation of Pbo_2 by altering Pao_2 or CPP can be used to optimize CPP management. In patients with acute ischemic stroke, impaired CPP brain tissue oxygen reactivity index predicts the development of malignant edema after middle cerebral artery infarction.

BRAIN OXYGEN AND OUTCOME

Several observational studies suggest that reduced brain oxygen is associated with worse outcome in acute brain injury in adults[23,28,33–37,49,71,89] and children,[38,39,71] although the strength of this relationship may depend in part on probe location relative to other disorders, such as, in normal white matter, the penumbra or in a contusion.[27,51] Episodes of brain tissue hypoxia may occur when CPP and ICP are normal,[23,28,30,69,71] so emphasizing the value of using both monitors. The number, duration, and intensity of $PbtO_2$ episodes less than 15 mm Hg, and any $PbtO_2$ values less than or equal to 5 mm Hg are associated with poor outcome after TBI.[23,28,33–37,49] A $PbtO_2$ less than 10 mm Hg is associated with 2-fold to 4-fold increase in both mortality and unfavorable outcome,[37] including neuropsychological performance[40,41]; this is important because ICP generally is associated with mortality alone rather than outcome. Furthermore, the development of compromised $PbtO_2$ is an independent variable associated with outcome rather than simply an indicator of disease severity.[28] Reduced $PbtO_2$ is also associated with outcome in SAH, although the observed relationship is less robust than in TBI.[40,41]

MANAGEMENT OF BRAIN OXYGEN

The association between outcome and $PbtO_2$ in observational series has led to the concept of

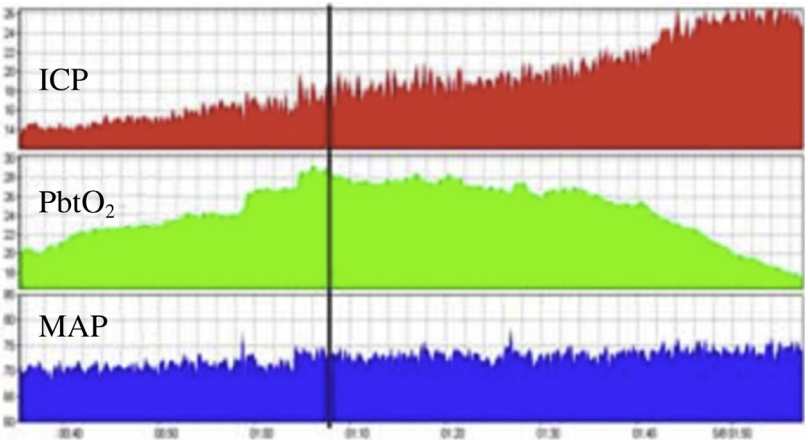

Fig. 2. Continuous monitoring of ICP, $PbtO_2$ and MAP, recorded over several hours, showing dynamic changes in ICP and its effect on $PbtO_2$. In particular, as ICP initially increases it is associated with an increase in $PbtO_2$. As ICP continues to increase, $PbtO_2$ eventually decreases (*vertical line*), which suggests the point at which ICP may be best treated in this individual (ie, targeted care), because it is at this point that the ICP increase is having an adverse effect on other measures of intracranial health. (*Adapted from* Rohlwink UK, Zwane E, Graham Fieggen A, et al. The relationship between intracranial pressure and brain oxygenation in children with severe traumatic brain injury. Neurosurgery 2012;70(5):1220–31; with permission.)

$PbtO_2$-based care. When severe TBI care is based on data from both a $PbtO_2$ and ICP monitor, some, but not all, observational series suggest that outcome is better than when just ICP-based care is provided[44–47]; this question is now being evaluated in a multicenter clinical trial. Oxygen delivery to the brain is the product of CBF and the arterial oxygen content and hence many variables can influence it (see **Box 2**). However, several physiologic factors suggest that even small changes in intracellular P_{O_2} can have a biological effect. First, neuronal mitochondria require an intracellular P_{O_2} as low as 1.5 mm Hg to maintain aerobic metabolism; this corresponds with a $PbtO_2$ between 15 and 20 mm Hg (ie, where treatment usually is initiated). Second, only oxygen dissolved in plasma can exchange between vascular and tissue compartments. However, oxygen is lipophilic and so can cross the endothelium (ie, influx through passive diffusion). Third, the apparent diffusion coefficient of oxygen is stable even with sustained ischemia. Fourth, cellular-mitochondrial gradients are small and, consistent with this, Zhou and colleagues[120] observed that normobaric hyperoxia administered after experimental TBI can restore mitochondrial ATP levels.

A $PbtO_2$ monitor does not influence outcome. Instead, information from a $PbtO_2$ monitor, like other monitors, should be interpreted and integrated with other data (eg, clinical examination, CT scan findings, ICP, CPP, pulmonary status, and hemoglobin). This approach allows patient-specific pathophysiology to be targeted and, in some circumstances, $PbtO_2$ to be used as a novel target or for otherwise unrecognized relationships to be defined, so moving away from empiric treatment alone. For example, in some patients who receive pressors to augment CPP in the presence of increased ICP, we have observed that induced hypotension (eg, nicardipine) instead has a better effect on physiology because it ameliorates an underlying hyperemia. In addition, the $PbtO_2$ data may permit avoidance of deleterious effects of other therapies (eg, hyperventilation) or avoid unnecessary treatment or overtreatment (eg, allow permissive intracranial hypertension in select patients who have a mild increase in ICP but otherwise normal cerebral physiology by defining when increased ICP adversely affects intracranial physiology) (**Fig. 2**). Although the relationship with outcome may vary with where the $PbtO_2$ probe is placed, treatment paradigms are largely based on the probe being in white matter that appears normal on head CT. In addition, the various techniques on how to manage $PbtO_2$ are still being elucidated. In large part, these therapies are based on understanding patient physiology (**Table 2**).

Table 2
Therapies to treat compromised brain oxygen

Frequently Used Therapy	Less Frequently Used Therapy
Adjust ventilator parameters to increase Pa_{O_2} Increase Fi_{O_2} (eg, 50%–60%) Increase PEEP	Ventriculostomy Continuous or intermittent CSF drainage
Transient hyperoxia 100% Fi_{O_2}	Blood transfusion
Augment CPP Colloid bolus Neosynephrine, dopamine	Neuromuscular paralysis Pancuronium, vecuronium
Pharmacologic analgesia and sedation Propofol, versed, ativan Fentanyl, morphine	Adjust ventilator rate Increase to lower $Paco_2$ (ICP) Decrease to increase $Etco_2$, $Paco_2$
Head position or avoid turning, certain positions	Pulmonary toilet and suction
ICP control Sedation, mannitol, IV lidocaine	Pentothal
Ensure temperature <38°C	DCH (or other cranial surgery)
	Labetalol, nicardipine

Abbreviations: DCH, decompressive hemicraniectomy; IV, intravenous; PEEP, positive end-expiratory pressure.
Data from Refs.[11,121,122]

Common therapies include changing head position, ventilator manipulation, transient increases in inspired oxygen, CPP augmentation, transfusion, and sedation, and these therapies are successful in correcting the abnormality in about 70% of episodes of reduced $PbtO_2$. Those patients who respond to a corrective therapy are more likely to have a better outcome[44,121,122] and treatments are best used in a cause-specific tier fashion rather than a stepwise linear fashion.

SUMMARY

$PbtO_2$ monitoring is a safe and reliable technique that permits continuous bedside evaluation of cellular function in patients with severe brain injury. Several variables including CBF, blood pressure, hemoglobin concentration, and systemic oxygenation influence $PbtO_2$. Reduced $PbtO_2$ (<20 mm Hg), often independent of ICP and CPP, is frequent after acute brain injury and can result from several

pathologic mechanisms (eg, increased ICP, ischemia, impaired oxygen extraction, anemia, or altered lung function). Information from a $PbtO_2$ monitor can guide the care of patients in the NCCU and help optimize CPP, $Paco_2$, Pao_2, and hemoglobin targets in individual patients, particularly when used in an integrated fashion with other monitors. Furthermore, observational data show an independent association between $PbtO_2$ and outcome. This finding has led to the concept of $PbtO_2$-based care to supplement and complement management based on ICP and CPP; whether this benefits outcome is still to be fully elucidated but early clinical series have produced promising results.

REFERENCES

1. Maas AI, Menon DK, Lingsma HF, et al. Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. J Neurotrauma 2011;29: 32–46.
2. Astrup J, Sorensen PM, Sorensen HR. Oxygen and glucose consumption related to Na+-K+ transport in canine brain. Stroke 1981;12:726–30.
3. Oddo M, Levine JM, Frangos S, et al. Brain lactate metabolism in humans with subarachnoid hemorrhage. Stroke 2012;43(5):1418–21.
4. Rosenthal G, Hemphill JC 3rd, Sorani M, et al. Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. Crit Care Med 2008;36:1917–24.
5. Brain Trauma Foundation, American Association of Neurological Surgeons; Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury. X. Brain oxygen monitoring and thresholds. J Neurotrauma 2007;24(Suppl 1):S65–70.
6. Stewart C, Haitsma I, Zador Z, et al. The new Licox combined brain tissue oxygen and brain temperature monitor: assessment of in vitro accuracy and clinical experience in severe traumatic brain injury. Neurosurgery 2008;63:1159–64 [discussion: 64–5].
7. Siegemund M, van Bommel J, Ince C. Assessment of regional tissue oxygenation. Intensive Care Med 1999;25:1044–60.
8. Dengler J, Frenzel C, Vajkoczy P, et al. Cerebral tissue oxygenation measured by two different probes: challenges and interpretation. Intensive Care Med 2011;37:1809–15.
9. Orakcioglu B, Sakowitz OW, Neumann JO, et al. Evaluation of a novel brain tissue oxygenation probe in an experimental swine model. Neurosurgery 2010;67(6):1716–22 [discussion: 1722–3].
10. Jaeger M, Soehle M, Meixensberger J. Brain tissue oxygen ($Ptio_2$): a clinical comparison of two monitoring devices. Acta Neurochir Suppl 2005; 95:79–81.
11. Maloney-Wilensky E, Le Roux P. The physiology behind direct brain oxygen monitors and practical aspects of their use. Childs Nerv Syst 2010;26(4): 419–30.
12. Hemphill JC 3rd, Knudson MM, Derugin N, et al. Carbon dioxide reactivity and pressure autoregulation of brain tissue oxygen. Neurosurgery 2001;48: 377–83.
13. Scheufler KM, Lehnert A, Rohrborn HJ, et al. Individual values of brain tissue oxygen pressure, microvascular oxygen saturation, cytochrome redox level and energy metabolites in detecting critically reduced cerebral energy state during acute changes in global cerebral perfusion. J Neurosurg Anesthesiol 2004;16:210–9.
14. Scheufler KM, Rohrborn HJ, Zentner J. Does tissue oxygen-tension reliably reflect cerebral oxygen delivery and consumption? Anesth Analg 2002;95: 1042–8.
15. Johnston AJ, Steiner LA, Coles JP, et al. Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. Crit Care Med 2005;33(1):189–95.
16. Menon DK, Coles JP, Gupta AK, et al. Diffusion limited oxygen delivery following head injury. Crit Care Med 2004;32:1384–90.
17. Longhi L, Valeriani V, Rossi S, et al. Effects of hyperoxia on brain tissue oxygen tension in cerebral focal lesions. Acta Neurochir Suppl 2002; 81:315–7.
18. Bailey RL, Quattrone F, Curtain C, et al. In: Proceedings of Neurocritical Care Society Annual meeting. The safety of multimodal monitoring in severe brain injury. Neurocritical Care Society Meeting. Montreal, 2011.
19. Siesjo BK, Siesjo P. Mechanisms of secondary brain injury. Eur J Anaesthesiol 1996;13:247–68.
20. Pennings FA, Schuurman PR, van den Munckhof P, et al. Brain tissue oxygen pressure monitoring in awake patients during functional neurosurgery: the assessment of normal values. J Neurotrauma 2008;25:1173–7.
21. Hoffman WE, Charbel FT, Edelman G. Brain tissue oxygen, carbon dioxide, and pH in neurosurgical patients at risk for ischemia. Anesth Analg 1996; 82(3):582–6.
22. Kiening KL, Unterberg AW, Bardt TF, et al. Monitoring of cerebral oxygenation in patients with severe head injuries: brain tissue Po_2 versus jugular vein oxygen saturation. J Neurosurg 1996;85(5): 751–7.
23. Chang JJ, Youn TS, Benson D, et al. Physiologic and functional outcome correlates of brain tissue

hypoxia in traumatic brain injury. Crit Care Med 2009;37(1):283–90.
24. Gopinath SP, Valadka AB, Uzura M, et al. Comparison of jugular venous oxygen saturation and brain tissue P_{O_2} as monitors of cerebral ischemia after head injury. Crit Care Med 1999;27:2337–45.
25. Gupta AK, Hutchinson PJ, Al-Rawi P, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg 1999;88:549–53.
26. Gopinath SP, Valadka A, Contant CF, et al. Relationship between global and cortical cerebral blood flow in patients with head injuries. Neurosurgery 1999;44:1273–8.
27. Ponce LL, Pillai S, Cruz J, et al. Position of probe determines prognostic information of brain tissue P_{O_2} in severe traumatic brain injury. Neurosurgery 2012;70(6):1492–502.
28. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery 2011;69(5):1037–45 [discussion: 1045].
29. Figaji AA, Zwane E, Thompson C, et al. Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part 2: relationship with clinical, physiological and treatment factors. Childs Nerv Syst 2009;25(10):1335–43.
30. Chen HI, Stiefel MF, Oddo M, et al. Detection of cerebral compromise with multimodality monitoring in patients with subarachnoid hemorrhage. Neurosurgery 2011;69(1):53–63 [discussion: 63].
31. Eriksson EA, Barletta JF, Figueroa BE, et al. Cerebral perfusion pressure and intracranial pressure are not surrogates for brain tissue oxygenation in traumatic brain injury. Clin Neurophysiol 2012; 123(6):1255–60.
32. Oddo M, Milby A, Chen I, et al. Hemoglobin concentration and cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage: a microdialysis study. Stroke 2009;40(4):1275–81.
33. Valadka AB, Gopinath SP, Contant CF, et al. Relationship of brain tissue P_{O_2} to outcome after severe head injury. Crit Care Med 1998;26: 1576–81.
34. van den Brink WA, van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. Neurosurgery 2000;46:868–76 [discussion: 76–8].
35. van Santbrink H, Maas AI, Avezaat CJ. Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. Neurosurgery 1996;38:21–31.
36. Sarrafzadeh AS, Kiening KL, Callsen TA, et al. Metabolic changes during impending and manifest cerebral hypoxia in traumatic brain injury. Br J Neurosurg 2003;17:340–6.
37. Maloney-Wilensky E, Gracias V, Itkin A, et al. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. Crit Care Med 2009;37(6):2057–63.
38. Figaji AA, Zwane E, Thompson C, et al. Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part 1: relationship with outcome. Childs Nerv Syst 2009;25(10):1325–33.
39. Narotam PK, Burjonrappa SC, Raynor SC, et al. Cerebral oxygenation in major pediatric trauma: its relevance to trauma severity and outcome. J Pediatr Surg 2006;41:505–13.
40. Meixensberger J, Renner C, Simanowski R, et al. Influence of cerebral oxygenation following severe head injury on neuropsychological testing. Neurol Res 2004;26:414–7.
41. O'Brien D, Frangos S, Watson E, et al. Brain oxygen and long-term functional and neurocognitive outcome after severe traumatic brain injury and subarachnoid hemorrhage. National Neurotrauma Annual Meeting, Las Vegas, 2010.
42. Meixensberger J, Vath A, Jaeger M, et al. Monitoring of brain tissue oxygenation following severe subarachnoid hemorrhage. Neurol Res 2003;25: 445–50.
43. Ramakrishna R, Stiefel M, Udoteuk J, et al. Brain oxygen and outcome in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 2008; 109(6):1075–82.
44. Spiotta AM, Stiefel MF, Gracias VH, et al. Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. J Neurosurg 2010;113:571–80.
45. Narotam PK, Morrison JF, Nathoo N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. J Neurosurg 2009;111: 672–82.
46. Martini RP, Deem S, Yanez ND, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. J Neurosurg 2009;111(4):644–9.
47. Nangunoori R, Maloney-Wilensky E, Stiefel M, et al. Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: a systematic literature review. Neurocrit Care 2012; 17(1):131–8.
48. Doppenberg EM, Zauner A, Watson JC, et al. Determination of the ischemic threshold for brain oxygen tension. Acta Neurochir Suppl 1998;71: 166–9.
49. Bardt TF, Unterberg AW, Hartl R, et al. Monitoring of brain tissue P_{O_2} in traumatic brain injury: effect of cerebral hypoxia on outcome. Acta Neurochir Suppl 1998;71:153–6.

50. Longhi L, Pagan F, Valeriani V, et al. Monitoring brain tissue oxygen tension in brain-injured patients reveals hypoxic episodes in normal-appearing and in peri-focal tissue. Intensive Care Med 2007;33:2136–42.
51. Sarrafzadeh AS, Kiening KL, Bardt TF, et al. Cerebral oxygenation in contusioned vs. nonlesioned brain tissue: monitoring of $Ptio_2$ with Licox and Paratrend. Acta Neurochir Suppl 1998;71: 186–9.
52. Hlatky R, Valadka AB, Gopinath SP, et al. Brain tissue oxygen tension response to induced hyperoxia reduced in hypoperfused brain. J Neurosurg 2008; 108(1):53–8.
53. Vik A, Nag T, Fredriksli OA, et al. Relationship of "dose" of intracranial hypertension to outcome in severe traumatic brain injury. J Neurosurg 2008; 109(4):678–84.
54. Stein DM, Hu PF, Brenner M, et al. Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome after severe traumatic brain injury. J Trauma 2011; 71(2):364–74.
55. Badri S, Chen J, Barber J, et al. Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury. Intensive Care Med 2012;38(11):1800–9.
56. Stein SC, Georgoff P, Meghan S, et al. Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. J Neurosurg 2010;112:1105–12.
57. Cremer OL, van Dijk GW, van Wensen E, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. Crit Care Med 2005;33(10): 2207–13.
58. Shafi S, Diaz-Arrastia R, Madden C, et al. Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. J Trauma 2008;64(2):335–40.
59. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 2012;367(26):2471–81.
60. Oddo M, Le Roux P. What is the etiology, pathogenesis and pathophysiology of elevated intracranial pressure?. In: Neligan P, Deutschman CS, editors. The evidenced based practice of critical care. Philadelphia: Elsevier Science; 2009. p. 399–405.
61. Aries MJ, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med 2012;40(8):2456–63.
62. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med 2002;30:733–8.
63. Jaeger M, Dengl M, Meixensberger J, et al. Effects of cerebrovascular pressure reactivity-guided optimization of cerebral perfusion pressure on brain tissue oxygenation after traumatic brain injury. Crit Care Med 2010;38:1343–7.
64. Hlatky R, Valadka AB, Goodman JC, et al. Patterns of energy substrates during ischemia measured in the brain by microdialysis. J Neurotrauma 2004; 21(7):894–906.
65. Vespa PM, O'Phelan K, McArthur D, et al. Pericontusional brain tissue exhibits persistent elevation of lactate/pyruvate ratio independent of cerebral perfusion pressure. Crit Care Med 2007;35(4): 1153–60.
66. Adamides AA, Rosenfeldt FL, Winter CD, et al. Brain tissue lactate elevations predict episodes of intracranial hypertension in patients with traumatic brain injury. J Am Coll Surg 2009;209:531–9.
67. Belli A, Sen J, Petzold A, et al. Metabolic failure precedes intracranial pressure rises in traumatic brain injury: a microdialysis study. Acta Neurochir (Wien) 2008;150:461–9.
68. Le Roux P, Lam AM, Newell DW, et al. Cerebral arteriovenous difference of oxygen: a predictor of cerebral infarction and outcome in severe head injury. J Neurosurg 1997;87:1–8.
69. Stiefel MF, Udoetek J, Spiotta A, et al. Conventional neurocritical care and cerebral oxygenation after traumatic brain injury. J Neurosurg 2006;105: 568–75.
70. Gracias VH, Guillamondegui OD, Stiefel MF, et al. Cerebral cortical oxygenation: a pilot study. J Trauma 2004;56:469–74.
71. Rohlwink UK, Zwane E, Graham Fieggen A, et al. The relationship between intracranial pressure and brain oxygenation in children with severe traumatic brain injury. Neurosurgery 2012;70(5): 1220–31.
72. Jaeger M, Schuhmann MU, Soehle M, et al. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. Crit Care Med 2006; 34:1783–8.
73. Lang EW, Czosnyka M, Mehdorn HM. Tissue oxygen reactivity and cerebral autoregulation after severe traumatic brain injury. Crit Care Med 2003;31: 267–71.
74. Muench E, Horn P, Bauhuf C, et al. Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. Crit Care Med 2007;35:1844–51.
75. Stocchetti N, Chieregato A, De Marchi M, et al. High cerebral perfusion pressure improves low values of local brain tissue O_2 tension ($Ptio_2$) in focal lesions. Acta Neurochir Suppl 1998;71: 162–5.

76. Marin-Caballos AJ, Murillo-Cabezas F, Cayuela-Dominguez A, et al. Cerebral perfusion pressure and risk of brain hypoxia in severe head injury: a prospective observational study. Crit Care 2005;9: R670–6.
77. Johnston AJ, Steiner LA, Chatfield DA, et al. Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury. Intensive Care Med 2004;30:791–7.
78. Oddo M, Levine JM, Frangos S, et al. Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. J Neurol Neurosurg Psychiatry 2009;80(8):916–20.
79. Sakowitz OW, Stover JF, Sarrafzadeh AS, et al. Effects of mannitol bolus administration on intracranial pressure, cerebral extracellular metabolites, and tissue oxygenation in severely head-injured patients. J Trauma 2007;62:292–8.
80. Stiefel MF, Heuer GG, Smith MJ, et al. Cerebral oxygenation following decompressive hemicraniectomy for the treatment of refractory intracranial hypertension. J Neurosurg 2004;101:241–7.
81. Weiner GM, Lacey MR, Mackenzie L, et al. Decompressive craniectomy for elevated intracranial pressure and its effect on the cumulative ischemic burden and therapeutic intensity levels after severe traumatic brain injury. Neurosurgery 2010;66: 1111–9.
82. Ho CL, Wang CM, Lee KK, et al. Cerebral oxygenation, vascular reactivity, and neurochemistry following decompressive craniectomy for severe traumatic brain injury. J Neurosurg 2008;108: 943–9.
83. Carmona Suazo JA, Maas AI, van den Brink WA, et al. CO_2 reactivity and brain oxygen pressure monitoring in severe head injury. Crit Care Med 2000;28:3268–74.
84. Coles JP, Minhas PS, Fryer TD, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med 2002;30:1950–9.
85. Clausen T, Scharf A, Menzel M, et al. Influence of moderate and profound hyperventilation on cerebral blood flow, oxygenation and metabolism. Brain Res 2004;1019:113–23.
86. Tolias CM, Reinert M, Seiler R, et al. Normobaric hyperoxia–induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. J Neurosurg 2004;101:435–44.
87. Nortje J, Coles JP, Timofeev I, et al. Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: preliminary findings. Crit Care Med 2008;36:273–81.
88. Diringer MN. Hyperoxia: good or bad for the injured brain? Curr Opin Crit Care 2008;14:167–71.
89. Oddo M, Levine JM, Kumar M, et al. Anemia and brain oxygen after severe traumatic brain injury. Intensive Care Med 2012;38(9):1497–504.
90. Smith MJ, Stiefel MF, Magge S, et al. Packed red blood cell transfusion increases local cerebral oxygenation. Crit Care Med 2005;33:1104–8.
91. Figaji AA, Zwane E, Kogels M, et al. The effect of blood transfusion on brain oxygenation in children with severe traumatic brain injury. Pediatr Crit Care Med 2010;11(3):325–31.
92. Leal-Noval SR, Munoz-Gomez M, Aerllano-Orden V, et al. Impact of age of transfused blood on cerebral oxygenation in male patients with severe traumatic brain injury. Crit Care Med 2008; 36:1290–6.
93. Le Roux P. Haemoglobin management in acute brain injury. Curr Opin Crit Care 2013;19(2):83–91.
94. Le Roux PD. Participants in the International Multidisciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Anemia and transfusion after subarachnoid hemorrhage. Neurocrit Care 2011;15(2):342–53.
95. Fletcher JJ, Bergman K, Blostein PA, et al. Fluid balance, complications, and brain tissue oxygen tension monitoring following severe traumatic brain injury. Neurocrit Care 2010;13(1):47–56.
96. Chen HI, Malhotra NR, Oddo M, et al. Barbiturate infusion for intractable intracranial hypertension and its effect on brain oxygenation. Neurosurgery 2008;63:880–6 [discussion: 6–7].
97. Thorat JD, Wang EC, Lee KK, et al. Barbiturate therapy for patients with refractory intracranial hypertension following severe traumatic brain injury: its effects on tissue oxygenation, brain temperature and autoregulation. J Clin Neurosci 2008; 15:143–8.
98. Johnston AJ, Steiner LA, Chatfield DA, et al. Effects of propofol on cerebral oxygenation and metabolism after head injury. Br J Anaesth 2003;91: 781–6.
99. Oddo M, Frangos S, Milby A, et al. Induced normothermia attenuates cerebral metabolic distress in patients with aneurysmal subarachnoid hemorrhage and refractory Fever. Stroke 2009;40(5): 1913–6.
100. Oddo M, Frangos S, Maloney-Wilensky E, et al. Effect of shivering on brain tissue oxygenation during induced normothermia in patients with severe brain injury. Neurocrit Care 2010;12(1):10–6.
101. Oddo M, Nduom E, Frangos S, et al. Acute lung injury is an independent risk factor for brain hypoxia after severe traumatic brain injury. Neurosurgery 2010;67(2):338–44.
102. Rosenthal G, Hemphill JC, Sorani M, et al. The role of lung function in brain tissue oxygenation

following traumatic brain injury. J Neurosurg 2008; 108(1):59–65.
103. Ledwith MB, Bloom S, Maloney-Wilensky E, et al. Effect of body position on cerebral oxygenation and physiologic parameters in patients with acute neurological conditions. J Neurosci Nurs 2010; 42(5):280–7.
104. Swanson E, Mascitelli J, Stiefel M, et al. The effect of patient transport on brain oxygen in comatose patients. Neurosurgery 2010;66:925–32.
105. Ekelund A, Reinstrup P, Ryding E, et al. Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 2002;144: 703–12 [discussion: 12–3].
106. Kett-White R, Hutchinson PJ, Al-Rawi PG, et al. Cerebral oxygen and microdialysis monitoring during aneurysm surgery: effects of blood pressure, cerebrospinal fluid drainage, and temporary clipping on infarction. J Neurosurg 2002;96: 1013–9.
107. Dudkiewicz M, Proctor KG. Tissue oxygenation during management of cerebral perfusion pressure with phenylephrine or vasopressin. Crit Care Med 2008;36:2641–50.
108. Stiefel MF, Heuer GG, Abrahams JM, et al. The effect of nimodipine on cerebral oxygenation in patients with poor-grade subarachnoid hemorrhage. J Neurosurg 2004;101:594–9.
109. Stiefel MF, Spiotta A, Udoetek J, et al. Intra-arterial papaverine used to treat cerebral vasospasm reduces brain oxygen. Neurocrit Care 2006;4:113–8.
110. Gelabert-Gonzalez M, Fernandez-Villa JM, Ginesta-Galan V. Intra-operative monitoring of brain tissue O_2 ($Ptio_2$) during aneurysm surgery. Acta Neurochir (Wien) 2002;144:863–6 [discussion: 6–7].
111. Hoffman WE, Charbel FT, Edelman G, et al. Brain tissue oxygenation in patients with cerebral occlusive disease and arteriovenous malformations. Br J Anaesth 1997;78:169–71.
112. Pennings FA, Bouma GJ, Kedaria M, et al. Intraoperative monitoring of brain tissue oxygen and carbon dioxide pressures reveals low oxygenation in peritumoral brain edema. J Neurosurg Anesthesiol 2003;15:1–5.
113. Hoffman WE, Edelman G. Isoflurane increases brain oxygen reactivity in dogs. Anesth Analg 2000;91:637–41.
114. van Santbrink H, vd Brink WA, Steyerberg EW, et al. Brain tissue oxygen response in severe traumatic brain injury. Acta Neurochir (Wien) 2003;145: 429–38 [discussion: 38].
115. Hoffman WE, Edelman G, Wheeler P. Cerebral oxygen reactivity in the dog. Neurol Res 2000;22: 620–2.
116. Soehle M, Jaeger M, Meixensberger J. Online assessment of brain tissue oxygen autoregulation in traumatic brain injury and subarachnoid hemorrhage. Neurol Res 2003;25:411–7.
117. Ang BT, Wong J, Lee KK, et al. Temporal changes in cerebral tissue oxygenation with cerebrovascular pressure reactivity in severe traumatic brain injury. J Neurol Neurosurg Psychiatry 2007;78: 298–302.
118. Jaeger M, Schuhmann MU, Soehle M, et al. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. Stroke 2007;38: 981–6.
119. Dohmen C, Bosche B, Graf R, et al. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. Stroke 2007;38:56–61.
120. Zhou Z, Daugherty WP, Sun D, et al. Protection of mitochondrial function and improvement in cognitive recovery in rats treated with hyperbaric oxygen following lateral fluid-percussion injury. J Neurosurg 2007;106(4):687–94.
121. Pascual JL, Georgoff P, Horan A, et al. Brain tissue hypoxia in traumatic brain injury: are most commonly used interventions successful at correcting brain tissue oxygen deficits? J Trauma 2011;70(3):535–46.
122. Bohman LE, Heuer GG, Macyszyn L, et al. Medical management of compromised brain oxygen in patients with severe traumatic brain injury. Neurocrit Care 2011;14:361–9.