FOCUS SESSION

The physiology behind direct brain oxygen monitors and practical aspects of their use

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Abstract

Introduction Secondary neuronal injury is implicated in poor outcome after acute neurological insults. Outcome can be improved with protocol-driven therapy. These therapies have largely been based on monitoring and control of intracranial pressure and the maintenance of an adequate cerebral perfusion pressure.

Discussion In recent years, brain tissue oxygen partial pressure ($PbtO_2$) monitoring has emerged as a clinically useful modality and a complement to intracranial pressure monitors. This review examines the physiology of $PbtO_2$ monitors and practical aspects of their use.

Keywords Brain oxygen · Cerebral blood flow · Clark electrode · Licox · Oxygen delivery

Introduction

Maintenance of adequate tissue oxygen is a fundamental objective in critical care medicine and after any form of brain injury. Therefore, the ability to assess tissue oxygenation and detect tissue hypoxia is vital in neurocritical care. Direct brain oxygen ($PbtO_2$) monitors have been used in the clinical environment since 1993 [1] but were first included in the treatment guidelines for severe traumatic brain injury (TBI) in 2007 [2]. Converging lines of evidence suggest that $PbtO_2$ monitoring is a safe, sensitive, and reliable

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diagnostic tool and may be an ideal complement to intracranial pressure (ICP) monitors [3–14]. In particular, we recently performed a systematic review of available English medical literature and found that brain hypoxia ($PbtO_2 < 10$ mmHg) after TBI is associated with a significant increase in both mortality and unfavorable outcome [6]. This suggests that efforts to improve $PbtO_2$ may improve outcome. Several review articles that describe $PbtO_2$ monitors and their use in different diseases have been published in recent years [15–19]. In this review, we will examine the physiology behind $PbtO_2$ monitors and practical aspects of their use.

Cerebral blood flow and oxygen delivery

The amount of O_2 that reaches a specific organ is the product of local blood flow and the arterial oxygen content (CaO_2). Arterial oxygen content depends on the hemoglobin (Hgb) concentration and how much it is saturated with O_2 (SaO_2). There also is a small amount of O_2 dissolved in blood. In addition, for oxygen to reach the cell, it needs to be released from Hgb and diffuse across the endothelium and interstitial space. Global systemic O_2 delivery therefore can be expressed by the following equation:

$$DO_2\,(ml\,O_2/min) = \text{Cardiac output}\,(L/min)$$
$$\times\{[Hb(g/L) \times SaO_2(\%) \times 1.39(ml\,O_2/Hgb)]$$
$$+(0.003 \times PO_2)\}$$

Oxygen delivery to the brain can be understood using the same equation but substitute cardiac output with cerebral blood flow (CBF). The Hagen–Poiseuille equation can be used to describe CBF and is based on cerebral

perfusion pressure (CPP), the length and caliber of the cerebral blood vessels, and the viscosity of blood:

$$CBF = (\pi r^4 \Delta P)/8\eta L$$
(where r= radius, P= pressure, L= length and η= viscosity)

From this equation, it is evident that homeostatic variations in the caliber of cerebral vessels (r in the Hagen–Poiseuille equation), in large part, regulate CBF and O_2 delivery to the brain in response to physiological and pathological stimuli. In the normal brain, most CBF and oxygen are consumed in the resting state to maintain neuronal membrane integrity. Small changes in local CBF and oxygen use are observed during activity, e.g., in the occipital cortex during a visual task. This change in CBF depends in part on the cytosolic $NADH/NAD^+$ ratio and the lactate pyruvate ratio (i.e., whether there is aerobic or anaerobic metabolism) that links activity-induced increases in glycolysis to signaling pathways for CBF regulation [20, 21].

CPP is derived from mean arterial pressure (MAP) and either jugular venous pressure or ICP, whichever is higher, i.e., CPP=MAP−ICP. The response of the cerebral blood vessels to CPP change is called CBF autoregulation. In the normal brain, cerebral arterioles constrict when CPP increases and dilate when CPP decreases to maintain a constant CBF. Autoregulation may be impaired in many patients with acute brain injury. The brain then becomes vulnerable to both hypo- and hyper-perfusion [22] since CBF is directly dependent on CPP when autoregulation is impaired. There are other stimuli that may alter cerebral vascular resistance and CBF. Both global and regional CBF are tightly coupled to brain metabolism, although in the injured brain, this coupling between CBF and cerebral metabolic rate ($CMRO_2$) often is disturbed. Thus, physiological changes that reduce $CMRO_2$, e.g., hypothermia or sedation, can reduce CBF, whereas pathological events, e.g., seizures, can increase CBF. In addition, CBF is influenced by variations in the partial pressures of carbon dioxide ($PaCO_2$) and, to a lesser degree, O_2 (PaO_2).

The effects of oxygen on CBF

While CBF responses to blood pressure and CO_2 are understood, less is known about O_2 regulatory mechanisms in the human brain and of its possible disturbances in TBI. Prolonged hyperoxia, e.g., hyperbaric oxygen (HBO), can cause cerebral vasoconstriction, including in normal brain, which may reduce perfusion and exacerbate neurologic damage [23–26]. This vasoconstrictive effect is independent of the arterial hypocapnia that accompanies breathing hyperoxic mixtures [27]. McDowall [28] also showed that, at a constant $PaCO_2$, CBF remains stable at high levels of PaO_2. The vessel response to changes in PaO_2 may depend

on nitric oxide metabolism [25]. The overall effects of hyperoxia on brain tissue oxygenation may depend on factors other than CBF and O_2 diffusion and in particular lung function. For example, transient hyperoxia can alter descending cortical inhibitory influences on the medullary respiratory control centers [29], whereas more prolonged hyperoxia may contribute to absorption atelectasis and so contribute to an intrapulmonary shunt and ventilation/perfusion (V/Q) mismatch [30] or alter hypoxic pulmonary vasoconstriction, a normal adaptive vasomotor response to hypoxia that shunts blood from poorly to better-ventilated lung segments [31]. In addition, the cerebral vascular and tissue response to hyperoxia may demonstrate regional differences associated with pathology, e.g., altered diffusion distance in focal lesions associated with cerebral edema [32].

The effects of hypoxia on CBF have been evaluated mainly in animal studies. In summary, these studies show that CBF does not change until PaO_2 is less than 50 mmHg when there is vasodilatation and an increase in CBF [33–35]. There have been fewer studies in humans [23, 36–38], but these studies also demonstrate an increase in CBF with moderate hypoxia through vasodilatation, i.e., cerebral hypoxemic vasodilatation. The PaO_2 (and associated $PaCO_2$) threshold at which this occurs is important to understand, since vasodilatation may increase ICP in injured patients with impaired compliance since cerebral blood volume can increase. In normal volunteers, transcranial Doppler studies suggest that middle cerebral artery blood flow velocity increases and cerebral vascular resistance decreases when SaO_2 is <90% [37]. This corresponds to a PaO_2<58 mmHg (7.9kPa) when the Hgb/oxygen dissociation curve is normal. The change in CBF when there is hypoxia associated with normocarbia does not depend on CPP [39], but instead, the response of the cerebral vessels may be mediated by a local mechanism sensitive to alterations in local tissue oxygen content [40].

Oxygen delivery

The physiology of O_2 distribution between the cerebral microvasculature and brain is not well understood. However the magnitude of O_2 flux is vital to neuron integrity. Oxygen delivery is directly proportional to both concentration and diffusivity. Hgb is nearly fully saturated at an arterial partial pressure of O_2 (PaO_2) of ~100 mmHg, which is the PaO_2 expected when a patient with normal lungs breathes ambient air at sea level (i.e., FiO_2 0.21). If blood flow stays constant, increasing O_2 transport to tissues can only be achieved under normal circumstances by increasing non-Hgb bound O_2, e.g., by increasing local PO_2, since only dissolved O_2 can cross the endothelium and blood–brain barrier. Many capillaries also are smaller than red blood cell corpuscles and need to dilate in response to local

tissue hypoxia, perhaps through release of nitric oxide. In addition, there is "acellular blood flow" in the brain. For example, studies in the rat cortex show that up to 20% of capillaries may not contain erythrocytes [41]. These various data suggest that non-Hgb O_2 transport may be important, and since the driving force for O_2 delivery to the cells (mitochondria) is the O_2 tension gradient [42], it provides a rationale for a clinical use of therapy designed to improve brain oxygen.

The Fick principle may be used to calculate the total amount of oxygen that diffuses across the blood–brain barrier per unit time, by subtracting the oxygen content in the jugular bulb from the arterial oxygen content ($AVDO_2$) and multiplying by the CBF [23]. The total amount of oxygen diffusing across the BBB per unit time can therefore be defined as: $CBF \times (CaO_2 - CvO_2)$. The oxygen content equation for artery $[CaO_2 = \%saturation_{art}(1.34)Hgb + 0.003(PaO_2)]$ and vein $[CvO_2 = \%saturation_{ven}(1.34)Hgb + 0.003(PvO_2)]$ can then be used to rewrite this equation to reflect oxygen diffusion into the brain as follows: $AVDO_2 = CBF\{[\%saturation_{art}(1.34)Hgb + 0.003(PaO_2)] - [\%saturation_{ven}(1.34)Hgb + 0.003(PvO_2)]\}$.

The risks and benefits of oxygen in the brain

Implicit in the ability to monitor $PbtO_2$ is the belief that improving $PbtO_2$ is associated with better outcome. Converging experimental and clinical data support the concept of brain oxygen-based therapy after acute brain injury [3, 7, 9, 14, 43–45]. There are many methods by which $PbtO_2$ can be improved; alterations in ventilator strategies to improve PaO_2 are one such method. While the benefits of O_2 have been known since the late eighteenth century so too has its potential toxicity. However, the concept of O_2 toxicity and the toxic threshold (exposure length and level) remain debated [46, 47].

Potential toxicity of oxygen in the brain

Few large-scale studies have addressed central nervous system (CNS) oxygen toxicity, and there is no consensus on the frequency of different symptoms among people exposed to hyperoxia. Our knowledge is mostly from animal HBO studies and from the diving and aviation industry that suggest CNS toxicity can occur when O_2 partial pressure is >2.0 atm absolute (ATA). Other studies suggest that lung toxicity is almost never seen when FiO_2 is <0.5 and takes at least 20–40 h before first manifest when FiO_2 is 1.0 [26, 48–52]. It also is clear that many factors, e.g., CO_2, physical activity, circadian rhythm, gender, and fluid status [51–55], can impact CNS oxygen toxicity. Several minor symptoms (e.g., nausea, dizziness, headache, disorientation, and blurred

vision) of CNS oxygen toxicity are difficult to define in patients with neurological disorders. However, CNS oxygen toxicity can be associated with seizures [49, 51, 55–57] or reduced CBF from vasoconstriction [24, 27, 58, 59]. In some [60], but not all animal models [61], and in humans [62] exposed to HBO, reactive oxygen species (ROS) may increase before CNS toxicity develops. Other human studies show that HBO does not induce lipid peroxidation. Since ROS can cause vasodilatation [63] and blood–brain barrier breakdown [64], cerebral edema and increased ICP may occur.

Benefits of increased PaO_2 to the brain

Several lines of evidence support the concept of $PbtO_2$-directed care after acute brain injury. An increase in $PbtO_2$ is associated with improved brain metabolism, measured with cerebral microdialysis [65] or positron emission tomography (PET) [66] in clinical TBI and with attenuated secondary brain damage in experimental TBI models [45]. Augmented oxygen delivery reduces infarct volumes in animal stroke models [43, 67], and high-flow oxygen therapy is associated with a transient improvement of clinical deficits and MRI abnormalities in patients with acute stroke [68]. In a small preliminary clinical study that included 53 severe TBI patients, we observed that $PbtO_2$-directed care was associated with less mortality than historical controls who had only ICP/CPP-directed treatment [9]. Brain oxygen-based therapy seeks only to correct compromised $PbtO_2$. An alternative "oxygen-based therapy" is to administer supranormal amounts of oxygen—i.e., HBO or normobaric hyperoxia. In severe TBI patients, HBO may reduce mortality, particularly when there is elevated ICP [69]. Experimental fluid percussion injury models in the rat suggest that normobaric hyperoxia (FiO_2 1.0) is as effective as HBO to restore mitochondrial and cellular adenosine triphosphate (ATP) levels; that is, from a mechanistic viewpoint, HBO is not always necessary [70]. Despite these promising studies, there remains debate about the physiological efficacy of normobaric hyperoxia with some PET [71] and microdialysis [72] studies, suggesting that it does not improve brain metabolism.

Direct brain oxygen monitors

Brain oxygen may be assessed using imaging (e.g., PET or magnetic resonance spectroscopy), jugular venous oximetry, near-infrared spectroscopy, or with direct $PbtO_2$ monitors. Direct $PbtO_2$ monitors are the most frequently used technique in clinical practice and two systems Licox (Integra Neuroscience, Plainsboro, NJ) and Neurotrend (Diametrics Medical, St. Paul, MN) have been widely used. There is a greater body of literature (twofold more

publications) that describes the Licox system, and it now is more commonly used since the Neurotrend device is no longer commercially available in most countries. While both monitors measure $PbtO_2$, there are differences. First, Licox is a Clark-type electrode that measures oxygen only. Neurotrend is a multi-parameter sensor that uses optical fluorescence to measure oxygen, PCO_2, and pH. The Neurotrend initially was based on a modified Clark-type electrode but, in 1998, changed design to a colorimetric method using optical fluorescence. This technology change makes it difficult to compare between old and more recent studies that describe the Neurotrend. Second, Licox catheters are precalibrated and so can be inserted without any pre-use calibration. However post-insertion stabilization (30 min to 2 h) is necessary before readings are reliable. By contrast, the Neurotrend monitor requires bedside calibration to a defined oxygen concentration. Third, the catheters have different lengths, and the Neurotrend needs to be inserted at a greater depth than the Licox catheter. Finally, the $PbtO_2$ threshold for critical cerebral ischemia is considered to be 10 mmHg for Licox [73], whereas for Neurotrend, it is 19 mmHg [74]. Less frequently used monitors include the Neurovent-P Temp® (Raumedic AG, Munchberg, Germany), which uses the same polagraphic technique as the Licox and the OxyLab pO_2® (Oxford Optronix Ltd., Oxford, UK) that measures $PbtO_2$ using optical fluorescence technology.

The Licox® $PbtO_2$ probe uses a closed polarographic Clark-type cell with reversible electrochemical electrodes. The Clark principle uses the electrochemical properties of noble metals to measure the oxygen content of tissue. The Clark electrode consists of a membrane covering a layer of electrolyte and two 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 molecules reduced on the cathode. This process is temperature-dependent, and so a temperature probe is provided with the $PbtO_2$ probe since brain and body (core) temperature may differ in patients with brain injury. A 1°C change in brain temperature may alter cerebral metabolism between 5% and 13% and so after CBF or ICP. The new Licox PMO probe includes both $PbtO_2$ and temperature in a single probe. The Licox monitor provides a measure of $PbtO_2$ in units of tension (mmHg). However, the standard measure of oxygen content usually is expressed in units of concentration (ml O_2/100 cc). Similarly, oxygen delivery and $CMRO_2$ are expressed in milliliter O_2/100 g brain per minute. The conversion factor, 1 m Hg=0.003 ml O_2/100 g brain, can be used to compare $PbtO_2$ to standard measurements of oxygen concentration and use.

What do brain oxygen monitors measure?

Exactly what $PbtO_2$ measures in humans is only now beginning to be understood, but in most studies, it appears that $PbtO_2$ varies with changes in arterial oxygen tension (PaO_2) or CBF [75–77]. However, the precise relationships between $PbtO_2$ and the balance between total oxygen delivery and cerebral oxygen metabolism are not well-characterized. This is important from a therapeutic perspective, since there is debate on whether $PbtO_2$ reflects CBF or oxygen extraction. Although $PbtO_2$ is influenced by factors that regulate CBF, and in particular CO_2 and MAP [75], a $PbtO_2$ monitor is not simply an ischemia monitor [78, 79]. Instead, it likely is a marker of the balance between regional oxygen supply and cellular oxygen consumption. It also is influenced by changes in diffusion distance between capillaries and cells and the proportion of arterioles and venules where the probe is placed [7, 32, 77]; that is, $PbtO_2$ may reflect oxygen diffusion rather than total oxygen delivery or cerebral oxygen metabolism. Other factors known to influence $PbtO_2$ include F_iO_2, arterial partial pressure of oxygen (P_aO_2), MAP, CPP, CBF, and Hgb concentration, to name a few, and it may be inversely correlated with oxygen extraction fraction on PET [80]. Importantly, a $PbtO_2$ monitor is different from a jugular bulb catheter that reflects the venous oxygen content in blood exiting the brain and so indicates the balance between oxygen delivery and oxygen utilization. By contrast, $PbtO_2$ is more a measurement of the oxygen that accumulates in brain tissue.

Recently, Rosenthal et al. [76] challenged 14 severe TBI with an increase in FiO_2 to 1.0 (oxygen reactivity), a 10 mmHg increase in mean arterial blood pressure (cerebral autoregulation), and a 10 mmHg decrease in $PaCO_2$ (CO_2 cerebral vascular reactivity). They made the following important observations: (1) PaO_2 and $PbtO_2$ both increased with an oxygen challenge. However, there was not a substantial change in oxygen delivery, and regional $CMRO_2$ remained unchanged. (2) During a MAP challenge, there was a small increase in CBF, and the mean $PbtO_2$ increased. A significant change in $CMRO_2$ was not observed. (3) Hyperventilation reduced CBF, and this increased $AVDO_2$. Although there were several study limitations, their data further suggest that $PbtO_2$ reflects the product of CBF and the arteriovenous difference in oxygen tension, $PbtO_2=CBF \times AVTO_2$; that is, the interaction between plasma oxygen tension and CBF is an important determinant of $PbtO_2$. This finding is consistent with experimental studies, which indicate that $PbtO_2$ does not simply reflect CBF [79], PET studies in human TBI that show that diffusion abnormalities can contribute to cerebral hypoxia [7], and microdialysis studies that indicate that increases in markers of anaerobic metabolism can occur independently from CPP [81]. In other words a $PbtO_2$

monitor can provide some insight into both ischemic and non-ischemic derangements of brain physiology after TBI. Rosenthal et al. [76] also compared the mean ratio of tissue to arterial oxygen concentration and the ratio of tissue to venous oxygen concentration. These values were was less than 2–2.5% consistent with Kety and Schmidt's original hypothesis that the concentration of oxygen in brain tissue is very small relative to the oxygen content of arterial and venous blood [23, 82].

Brain oxygen

The adult brain weighs about 2% of body weight, yet consumes about 20% of the O_2 consumed by the entire body. Greater than 90% of this O_2 is used by the mitochondria to produce ATP that is integral to cell function [83]. Before energy metabolism can take place, brain cells must be supplied with O_2 and glucose, which practically is the only fuel for the brain. Only then, and with normal mitochondrial function, can sufficient energy (ATP) be produced. 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. Mitochondrial dysfunction plays a significant role in cellular failure after brain injury [84]. Physiological studies suggest that mitochondria need an O_2 concentration of 1.5 mmHg to produce ATP [82, 85]. This level corresponds to a $PbtO_2$ between 15 and 20 mmHg. A similar $PbtO_2$ level is observed using 7 T MRI techniques and fluorescent quenching techniques. Consequently, even a small change in intracellular PO_2 ($PbtO_2$-based therapy) can have a true biologic effect [86] and from a physiological perspective suggests that a treatment threshold of 20 mmHg is reasonable. This is consistent with recent studies in patients undergoing deep brain stimulation that suggest that normal $PbtO_2$ levels are about 25 mmHg [87] and clinical TBI studies that demonstrate the peak for relative risk of a poor outcome, including poor functional outcome 6 months after injury, was associated with $PbrO_2 < 20$ mmHg [3].

Brain oxygen in acute brain injury

Meixensberger et al. [1] introduced the concept that monitoring brain tissue oxygenation may influence therapy in 1993. The US Food and Drug Administration approved the use of a direct $PbtO_2$ monitor in 2001. This technology enables clinicians to measure $PbtO_2$, and so initiate therapies to optimize brain tissue oxygenation, before secondary ischemic injury occurs. In particular, a $PbtO_2$ monitor appears to discriminate reliably between normal oxygenation, threatened ischemia, and critical ischemia. For example, Scheufler et al. [79], in a rabbit model where brain physiology was measured using a $PbtO_2$ monitor, microdialysis, cytochrome oxidase redox levels, local CBF, and brain electrical activity, found that $PbtO_2$ discriminated between normal, moderately reduced perfusion and frank ischemia when CPP and ICP were varied. These investigators also found that the $PbtO_2$ monitor reliably predicted the transition to energy failure in a global CPP insult model. Accumulating clinical evidence suggests that $PbtO_2$ monitors may be an ideal complement to ICP monitors, are more than an "ischemia" monitor [76, 78] and can be useful in TBI management [2–19]. Values between 20 and 40 mmHg are regarded as normal, whereas reductions (<15 mmHg) are associated with ischemia. In addition, poor outcome is associated with the number, duration, and intensity of cerebral hypoxic episodes ($PbtO_2 < 15$ mmHg) and any $PbtO_2$ values ≤ 5 mmHg [4, 8, 11–14]. Decreases in $PbtO_2$ also are not benign and are associated with independent chemical markers of brain ischemia [88]. These $PbtO_2$ reductions are common and occur in up to 70% of patients including when ICP and CPP are normal [10, 11, 14, 89]. For example, in a prospective observational study of patients with severe TBI, we observed that only 33% of episodes of compromised $PbtO_2$ were associated with CPP<65 mmHg during their ICU course [89]. In the early hours after resuscitation, compromised $PbtO_2$ or hypoxia are common and are observed in 45% and 25% of patients despite attaining CPP levels stipulated in the Severe TBI Guidelines [10].

Brain oxygen in pediatric brain injury

Most clinical $PbtO_2$ studies have been in adults. In addition, the vast majority of clinical studies that address pediatric $PbtO_2$ include few patients and so age-related differences in physiologic variables often are indiscernible [90, 91]. In a larger prospective cohort of 52 children (<15 years old) with severe TBI, Figaji et al. [92–94] have made the following important observations: (1) Reduced $PbtO_2$ is poorly predicted by clinical and physiological (e.g., ICP, CPP, SaO_2, PaO_2, and Hb) factors commonly measured in pediatric ICU care; (2) adherence to physiological targets for ICP control, CPP management, and respiratory function may not avoid brain hypoxia in all patients; (3) reduced $PbtO_2$ is an independent factor associated with mortality and unfavorable outcome in children with severe TBI; and (4) $PbtO_2$ is reduced to lower values and for a longer duration of time in patients with poor outcome. Together, these data suggest that $PbtO_2$ monitors may play an important role in the care of pediatric brain injury.

Practical aspects of brain oxygen monitor use

Introduction of new technology

The task of introducing a new technology, e.g., a PbtO$_2$ monitor, in the ICU can be exciting but may be met with reticence, in part because of unfamiliarity with the new and different technology or management strategies. In addition, inappropriate use of new technology can be costly to an institution. It is important therefore to identify a physician and nurse champion. Their role is to join forces to promote evaluation of the technology at bedside, design a care and management plan, and support staff education and device evaluation. Continued use of a new technology such as Licox requires that staff in all disciplines that will be potentially impacted by its use understand the benefit and application of the technology. A phased implementation of PbtO$_2$ monitoring with a core group of clinical experts from the pilot unit who then support bedside implementation and provide 24-h technical and clinical support to the nursing and physician staff often allows successful hospital wide use, i.e., there should be ample time to present and educate the key participants, including nursing staff, respiratory therapy, and staff in other areas such as the operating room, radiology, or angiography suites before the new technology becomes commonplace [95]. ICU nurses play an important role in introduction of the new device, since, often, it is they who ensure the collaboration between subspecialists [96].

Clinical Practice Guidelines (CPGs) also can play an important role when introducing new technology at the bedside [97]. They provide a framework that allows for continuity of care and limits practice variability in an attempt to provide or develop a consistent standard of care. In addition, the CPG can serve as a resource in the management of a specific diagnosis or patient population, e.g., when to use a PbtO$_2$ probe, PbtO$_2$ location, goals of therapy, interventions, evaluation, and cessation of monitoring. The initial CPG is based on a thorough literature review for established best practices and after consultation with colleagues in centers with established multimodality monitoring programs. It also is important for the team to review each case in the beginning to review practice interventions and evaluate and edit the bedside protocols based on experience. This section will discuss the practical considerations to bedside PbtO$_2$ monitoring.

Patient selection and the decision to use a PbtO$_2$ monitor

A PbtO$_2$ monitor is intended for patients that are at risk for secondary neuronal injury. This includes patients with severe TBI, aneurysmal subarachnoid hemorrhage, malignant stroke, severe cerebral edema associated with tumors or infection, or any neurologic disease process where cerebral hypoxia and/or ischemia are suspected or likely. At our institution, we place a PbtO$_2$ monitor in patients with acute neurologic injury and a Glasgow Coma Scale of 8 or less. The device should not be used alone. Instead, a PbtO$_2$ monitor is intended to provide information about trends and be used with other monitors, in particular ICP and blood pressure, the clinical examination, and other data to develop individualized and targeted care. The Licox® CMP system includes a triple lumen bolt to monitor PbtO$_2$, ICP, and brain temperature. Absolute contraindications to use include an infection at the intended insertion site or coagulopathy that cannot be corrected. Relative contraindications include a platelet count between 75,000 and 100,000 or disease states that predispose to coagulation disorders, e.g., liver disease, renal disease, or severe hypothermia among others.

The Licox CMP system is intended for use by a qualified physician. Generally, it is a neurosurgeon who inserts the device, but in several institutions, neuro-intensivists place a Licox. The Licox system is compatible with CT. However, it may not pass the safety range for every MRI. If a patient requires an MRI, the entire device needs to be removed from the patient in those institutions where it is determined that the bolt system in incompatible with MRI. This compatibility should be established when the Licox CMP system is introduced to practice.

Insertion

Informed consent, including a discussion about the goals, duration, and expected outcomes of multi-modality monitoring, should be obtained from family members when they are available. Admission imaging studies should be studied to determine where to place the monitor. In general, we place the probe into normal appearing white matter on admission head CT in the frontal lobe on the side of maximal pathology. Where no asymmetry is observed on head CT, e.g., diffuse edema or diffuse axonal injury, the Licox is placed in the right frontal area. Following aneurysm rupture, the Licox may be placed ipsilateral to the ruptured aneurysm or on the side where the subarachnoid hemorrhage is thickest in an attempt to monitor the brain region most at risk to vasospasm. When a PbtO$_2$ monitor is in "undamaged" brain areas, the values can be extrapolated to evaluate global oxygenation even though the probe only measures local PbtO$_2$ [98, 99]. Perilesional or penumbral areas may show the most metabolic disturbance and be most at risk for secondary injury and so may be a preferred insertion point in some patients. However, we have observed that such placement in some patients may alter the threshold at which PbtO$_2$ is treated. In these patients, a perfusion CT scan or other blood flow study may help understand treatment thresholds in the region of the PbtO$_2$ probe. The monitor should not be placed into an already infracted area or into a

hematoma or contusion. In addition, the bolt should not be placed through a craniotomy bone flap.

Before insertion, the calibration of the device should be checked according to manufacturer's instructions by reading the $PbtO_2$ value at room temperature. Insertion may occur at the bedside in the ICU or in the operating room. A good light source, e.g., a headlight, is valuable. When the Liocx monitor is prepared for insertion, the probe-specific smart card must be secured and placed in the stand-alone monitor after verifying that the card and probe number are identical. If the smart card is discarded with the probe packaging before use, the Liocx monitor cannot be used. Incorrect measurements occur if the incorrect smart card is used. Sterile technique and general surgical precautions should be used. The Licox device is pre-packaged, and surgical insertion kits are available. The bolt entry point generally is in the mid-pupillary line anterior to the coronal suture (i.e., where a ventriculostomy is placed). The dura can be opened with a careful last twist of the drill but preferably with an 11 blade or less frequently a needle. The bolt is secured so that its end is in the subarachnoid space and the three probes (temperature, ICP, and $PbtO_2$) placed.

Post-insertion

Once each probe is placed, they are connected to their specific monitor cable. It is important that these cables are secured to prevent inadvertent dislodging of the intracranial monitoring device. Ideally two tension points should be established to secure the device to the patient. The first tension point is directly at the patient's head. For example, tape the base of the conical dressing and the cables to an arm board at the insertion site. The second tension point is at the patient's shoulder. The Licox cables should be brought down from the head to the shoulder and anchored in place with a dressing, allowing enough room for adequate rotation without impediment of the patient's neck. These methods will ensure that the Licox probe cables are not "hanging" or "pulling" at the insertion site.

The Licox $PbtO_2$ probe is subject to an "insertion effect," i.e., readings in the first 30 min to 2 h may be inaccurate. In most patients, waiting 1 h before using the $PbtO_2$ data is sufficient to allow probe stabilization. When the value is unexpectedly low and cannot be explained by patient pathophysiology or there is a question about probe function or placement, an oxygen challenge test should be performed. To do this, place the ventilator FiO_2 on 100% for 2 to 5 min. An accurate probe will demonstrate an increase in $PbtO_2$; the final value after 5–10 min should be >20 mmHg. If there is no response to increased FiO_2, a head CT should be obtained to confirm correct probe placement. At some institutions, oxygen challenge tests are routine and repeated daily to determine oxygen reactivity. The ICP and brain tissue temperature values can be used immediately after probe placement.

Table 1 Interventions that can be used to correct $PbtO_2$ values

$P_{bt}O_2$ Low (<20mmHG)		
Increased Demand	⬆ ICP	Treat ICP - diuretics, CSF drainage, sedation (barbiturates, Propofol), craniotomy
	Pain	Give pain medication
	Shivering	Stop shivering- Demerol, Thorazine, paralytic
	Agitation	Give sedation
	Seizures	Give Benzodiazapine & adjunct anticonvulsant
	Fever	Treat fever- Tylenol, NSAID, cooling devices
Decreased Delivery	Hypotension ⬇ (CPP)	Isotonic fluids (NS or hypertonic saline), vasopressors
	Hypovolemia	Isotonic fluids (NS or hypertonic saline), blood replacement
	Anemia	Blood replacement
	Hypoxia	Increase FIO2, PEEP, pulmonary toilet

$P_{bt}O_2$ high (>50mmHG)		
Increased delivery	Hyperdynamic (hyperemic)	Hyperventilation?
Decreased demand	Hypothermia	Normothermia
	Sedatives Anesthesia Paralysis	Decrease sedation, anesthesia, or paralysis as needed but treatment may not be necessary

Patient transport

Intrahospital transport of critically ill patients for diagnostic or therapeutic procedures is part of intensive care. However, transport carries an inherent risk, and complications or mishaps do occur. In addition, we have observed that transport can reduce $PbtO_2$ [100]. It is important to establish a process of patient transport to prevent device dislodgement. The blue and green Licox cables should be disconnected from the stand-alone monitor, coiled and taped to the patient's chest. The Licox CMP smart card must never be removed from the Licox monitor if remote trending is not in the plan. Upon return from transport, the blue and green cables can be plugged into their appropriate slots on the Licox module that automatically recalibrates itself so continuous monitoring of trends can resume.

Patient management

Brain oxygen values are relative within an individual and should not be used as the sole basis for decisions about diagnosis or therapy. Baseline nursing assessments and documentation of neurological status, hemodynamic parameters, core temperature, and various monitor trends must be continued every hour and whenever there is a change in patient status. In addition, patient care including patient position, suctioning, family or medical teams at the bedside, medication use, e.g., Mannitol, sedation or paralytics, ventilator changes, and bedside procedures among others should be recorded. This allows the healthcare team to accurately follow trends in the patient's status and initiate $PbtO_2$-directed therapy based on the individual patient's trends and needs.

Normal $PbtO_2$ values are between 20 and 35 mm Hg [87, 101]. A $PbtO_2 < 15$ mmHg is a critical threshold associated with cerebral ischemia and poor outcome. Values <10 mmHg are associated with a fourfold increase in mortality and poor outcome, $PbtO_2 < 5$ mm are associated with cellular death and up to 90% mortality, and sustained $PbtO_2$ values of 0 mmHg may occur in brain death [6, 11, 13, 14, 18, 73, 79, 102, 103]. In addition, the intensity and duration of compromised $PbtO_2$ and how it responds to treatment is associated with outcome. For example, we have observed that mortality is greater than 80% among patients with brain hypoxia when they do not respond to therapy but about 50% when they do [104]. While the absolute $PbtO_2$ threshold at which treatment should be started is debated, there is a growing consensus that, in adults, $PbtO_2$ should be maintained >20 mmHg and therapy started when it is less than this [3]. A $PbtO_2$ threshold of 15 mmHg also is used in some institutions [2]. The significance of "supranormal" $PbtO_2$ (>40 mmHg) is unclear as is whether it should be treated. The $PbtO_2$ values are not to be used in

isolation; in these patients, therapy preferably should maintain ICP <20 mmHg and jugular venous oxygen saturation ($SjvO_2$), when a retrograde jugular catheter is used, between 55% and 75%. It is important to realize that $PbtO_2$ and $SjvO_2$ do not always correlate since they measure different aspects of brain oxygenation.

Table 1 lists interventions that can be used to correct $PbtO_2$ values. The therapy should be used in a cause- and patient-specific manner. Table 2 lists the various therapies we have used in our ICU.

Troubleshooting

Troubleshooting any device connected to a patient is an essential responsibility of the ICU nurse. The CPG and Operations Manual should be used to guide this process. It is recommended that a laminated pocket card with the most important facts for device insertion, monitoring, and technology maintenance be created and secured to the Licox monitor at the bedside [97, 105, 106].

Table 2 Therapies used in our ICU to treat compromised brain oxygen

Frequently used therapy	Less frequently used therapy
Adjust ventilator parameters to increase PaO_2	Ventriculostomy
Increase FiO_2 (e.g. 50 to 60%)	Continuous or intermittent CSF drainage
Increase PEEP	Blood transfusion
Transient Normobaric Hyperoxia 100% FiO_2	Neuromuscular paralysis
Augment CPP	Pancuronium, vecuronium
Colloid bolus	Adjust ventilator rate
Neosynephrine, dopamine	Increase to lower $PaCO_2$ (ICP)
Pharmacologic analgesia and sedation	Decrease to increase $EtCO_2$, $paCO_2$
Propofol, versed, ativan	Pulmonary toillette and suction
Fentanyl, morphine	Penthothal (barbiturate burst suppression)
Head position or avoid turning, certain positions ICP control	Labetalol
Sedation, mannitol, IV lidocaine, HTS	
Insure temperature <38°C	
DC (or other cranial surgery)	

$PbtO_2$ therapy is targeted and occurs in a physiology based parallel process with ICP management. Therapies are titrated to effect and often occur in various combinations rather than single therapies. *PaO₂* partial pressure of oxygen in arterial blood, *FIO₂* fraction of inspired O_2, *PEEP* positive end-expiratory pressure, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure, *CSF* cerebrospinal fluid, *PaCO₂* partial pressure of carbon dioxide in blood, *EtCO₂* end tidal carbon dioxide, *HTS* hypertonic saline, *DC* decompressive craniectomy

Safety

Use of a Licox PbtO$_2$ monitor is safe: The complication rate (hematomas associated with the device or infection) is about 1% [6]. This complication rate compares very favorably with other parenchymal monitors, e.g., a Camino ICP monitor. Hematomas usually are associated with technical difficulties during insertion rather than the device.

Removal of PbtO$_2$ monitor

Brain oxygen monitors may be removed when any of the following conditions are met: (1) The patient awakens from coma (motor GCS=6) or if aphasic a mGCS of 5; (2) there is a medical indication for removal of the monitor (such as infection or bleeding associated with the catheter). The device may be replaced if still required medically. (3) ICP is normal (<20 mmHg) for 24 h without treatment. (4) PbtO$_2$ values are >20 mmHg for >48 h, and ICP is normal. The Licox CMP system should be removed by a physician or credentialed healthcare provider (nurse practitioner/physician's assistant) according to individual hospital policy. The winged cap should be loosened and unscrewed from the bolt housing. The three probes (ICP, PbtO$_2$, and temperature), followed by the triple-lumen sheath and then the bolt are removed. The insertion site is sutured and a sterile dressing applied. Dispose of the single-use probes and Licox CMP bolt system are disposed of but do not dispose the blue and green cables. These cables are cleaned and attached to the monitor for storage. Blood and debris may be removed from the cables with a towel and aqueous soap solution that also may contain formaldehyde. Disinfectants containing a high percent of alcohol or phenol will damage the cables.

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