Brain Tissue Oxygen Monitoring in Children—A Review

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Abstract
Brain tissue oxygen monitoring is a relatively new technique for continuous measurement of focal brain tissue oxygen tension (PbtO$_2$). There are several studies of PbtO$_2$ monitoring in adult patients but few in children. The goal is the prevention, or early detection and treatment, of secondary insults. Episodes of low PbtO$_2$ are associated with worse outcome, and treatment directed by PbtO$_2$ may benefit patients, but there is no Class I evidence as yet. What determines PbtO$_2$ is multifactorial and the underlying pathophysiological events affecting PbtO$_2$ may be complex. The clinician using this technology must understand the technical and physiological aspects, as well as the limitations, of PbtO$_2$ monitoring if there is to be any clinical benefit. However, whether PbtO$_2$ monitoring delivers overall benefit across centers of different expertise requires a randomised controlled trial. This review examines the current literature on PbtO$_2$ monitoring with a focus on children, the important technical and physiological factors, and an approach to using a PbtO$_2$ monitor.

Keywords
Brain tissue oxygen, children, traumatic brain injury, head trauma, subarachnoid hemorrhage, brain perfusion, technical

The introduction of brain tissue oxygen (PbtO$_2$) monitoring into the neuro-intensive care unit (NICU) has created exciting opportunities for intervention but requires many questions to be answered before it can achieve widespread adoption. This article will cover the technical aspects of PbtO$_2$ monitoring, the physiological correlates of PbtO$_2$, the published literature on PbtO$_2$ monitoring in children, and practical approaches to monitoring and managing PbtO$_2$ in the clinical situation.

PbtO$_2$ is measured and monitored continuously using a thin catheter inserted into brain parenchyma. It is increasingly being used in the management of patients with acute neurological pathology, most commonly severe traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), to complement other forms of monitoring. The ease of use and the potential for continuously monitoring the adequacy of brain oxygenation and measuring its response to intervention in real-time have contributed to its growing popularity in the NICU, as clinicians try to avoid or ameliorate secondary injury to maximize the chance of a favorable outcome.

Post mortem$^7$ and clinical studies$^{14}$ suggest that secondary brain hypoxia–ischemia contributes significantly to poor outcome after TBI; therefore, the rationale for monitoring appears to be strong. The purposes of monitoring oxygenation of the brain are four-fold: to detect episodes of threatened brain ischemia/hypoxia early and respond immediately; to detect the adverse effects of therapy directed at other physiological parameters (e.g. hyperventilation for increased intracranial pressure [ICP]); to titrate therapy (e.g. optimizing cerebral perfusion pressure); and to assist interpretation of perturbations of other modalities, such as ICP. However, it is only recently that methods that enable monitoring of some aspects of brain oxygenation have begun to be used regularly in the NICU, of which PbtO$_2$ arguably appears to be the most promising.

Alternatives for continuous oxygenation monitoring such as jugular venous saturation (SjVO$_2$) and near-infrared spectroscopy (NIRS) appear to have more limitations, which has restricted wider use. SjVO$_2$ monitoring has a reduced time-of-good-quality-data$^5$ (related to artifacts and repeated calibrations required) and may miss focal ischemia.$^{12}$ NIRS is popular for somatic monitoring and for cerebral monitoring when the brain is normal (for example in cardiac anesthesia), but it may be more limited in neurocritical care, where a wet chamber between the optode and skin, subdural air after craniotomy, extracranial contamination, scalp swelling, subdural blood, SAH, and brain swelling may reduce the reliability of the signal and therefore its clinical application.$^{13}$ Normal NIRS signals have been found with complete brain ischemia.$^{10}$

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However, there are also limitations of PbtO$_2$ monitoring that need to be considered. The catheter monitors a restricted area of brain tissue and the determinants of PbtO$_2$ are still debated and require further examination. Although the association between low PbtO$_2$ and poor outcome appears to be strong, it is much less certain whether PbtO$_2$-directed therapy improves outcome. Lastly, while several studies of PbtO$_2$ monitoring in adult patients have been conducted, much less is known about PbtO$_2$ monitoring in children.

Technical Aspects of Brain Tissue Oxygen Monitoring

Three PbtO$_2$ devices have been produced commercially: Licox (Integra Neurosciences, Plainsboro, NJ), Neurotrend (Codman, Raynham, MA), and Neurovent-PTO (Raumedic, München, Germany). Of these, the Licox system is most widely used, and also measures brain temperature in the same catheter (IT2). The Neurotrend is no longer commercially available. The Neurovent-PTO is novel in that it also measures ICP, but is new on the market and few data on its clinical reliability are currently available. The Licox system is based on a Clarke-type polarographic cell containing two electrodes covered by a membrane. The amount of O$_2$ diffusing across this membrane depends on local tissue PO$_2$ and determines the electrical current between the two electrodes. Several studies have confirmed the reliability of the PbtO$_2$ signal, in vitro accuracy, and low sensitivity and zero drift over time. The sampling area is approximately 14–17 mm$^3$. Local tissue damage is minimal and complications are rare. The time-of-good-quality-data is in the region of 99%, repeat calibration is not required and artifacts are unusual. Although the PbtO$_2$ readings are usually stable within one hour of insertion, sometimes the adaptation period may take up to two hours.

Normal and Abnormal Brain Tissue Oxygen Values

Normal values in humans are not precisely known. Because the PbtO$_2$ value is influenced strongly by local cerebral blood flow (CBF), the value varies widely depending on the metabolic activity and diffusion characteristics of the region being monitored. However, variability is reduced during periods of ischemia. Extrapolation from studies that have measured PbtO$_2$ in animals and human studies monitoring relatively normal brain suggest that normal values for PbtO$_2$ are around 25–30 mmHg. Studies of PbtO$_2$ in aneurysm surgery demonstrate the decline in PbtO$_2$ associated with ischemia due to temporary clipping. Poor outcome in TBI patients is more likely when PbtO$_2$ falls progressively below 20 mmHg. Scheufler et al. demonstrated in an animal model that CBF levels below 20 ml/100g/minute correlate with PbtO$_2$ levels below 10 mmHg. This also appears to be true in injured or when there is a global insult, monitoring PbtO$_2$ in frontal white matter appears to provide a useful approximation of global changes in brain oxygenation. If there is focal injury, many clinicians aim to monitor tissue in the penumbra of the lesion, as PbtO$_2$ is usually lower in these tissues. Similar focal/global principles are relevant also to monitoring with microdialysis. PbtO$_2$ values require interpretation based on tissue being monitored, for both generalization of the results to the rest of the brain and interpretation of the PbtO$_2$ response to intervention. Peri-contusional (or peri-lesional) brain may demonstrate altered pathophysiological responses to interventions that require a different interpretation compared to ‘non-lesioned’ brain.

Factors that Influence Brain Tissue Oxygen

The best descriptor of what PbtO$_2$ monitoring in the brain reflects is debated. Often considered a measure of the balance between supply and demand of oxygen in the tissues, it has variably been associated with CBF, product of blood flow and oxygen content, mean transit time of blood through the brain, arteriovenous difference of oxygen, and end-capillary venous PO$_2$. In general terms, it is probably best considered a measure of factors that affect both the perfusion and diffusion characteristics of brain tissue. Some of the important practical factors that influence PbtO$_2$ are discussed below.

Brain Tissue Oxygen and Arterial Partial Pressure of Oxygen

Being a measure of the partial pressure of oxygen, PbtO$_2$ is significantly affected by the arterial partial pressure of oxygen (PaO$_2$). Therefore, even in conditions where arterial blood is near full saturation and increased PaO$_2$ does not change oxygen content significantly, increased PaO$_2$ is followed by increased PbtO$_2$. Accordingly, the arteriovenous difference of oxygen strongly influences PbtO$_2$. Similarly, progressive systemic hypoxia leads to a decline in PbtO$_2$ and increased anaerobic metabolism. A potential limitation is that the ventilator fraction of inspired oxygen (FiO$_2$) setting may significantly influence the PbtO$_2$ reading in the absence of substantial changes in oxygen delivery. On the other hand, dissolved oxygen may be preferentially used for tissue oxygenation and increased tissue oxygen pressure may overcome tissue barriers to diffusion and may improve metabolism. The relative benefits of hyperoxia on PbtO$_2$ and metabolism in TBI, however, are currently debated.

Brain Tissue Oxygen and Arterial Partial Pressure of Carbon Dioxide

PbtO$_2$ varies with changes in arterial partial pressure of carbon dioxide (PaCO$_2$) if CO$_2$ reactivity is preserved, largely secondary to the vasoactive effects of PaCO$_2$. Therefore, hypocarbia may induce or worsen cerebral ischemia, and relative hypercarbia may improve local CBF and therefore local oxygenation in areas at risk for ischemia. However, if hypercarbia significantly increases cerebral blood volume, and therefore ICP, the reduced cerebral perfusion pressure (CPP) may have the opposite effect on PbtO$_2$. This, and variations in the strength of CO$_2$ reactivity in the cerebral vessels, as well as different responses in abnormal tissue, may account for occasional ‘paradox’ reactions of PbtO$_2$ in response to CO$_2$ changes. Moderate hyperventilation without monitoring brain oxygenation is no longer recommended.

Brain Tissue Oxygen and Intracranial Pressure

Increased ICP may reduce PbtO$_2$, either by the local tissue pressure effect or by reduction of cerebral perfusion pressure (CPP). Reports of
decompressive craniectomy and barbiturate therapy in adult TBI have demonstrated improved PbtO2 after relief of high ICP. However, when results are pooled the overall relationship between ICP is poor because PbtO2 does not depend on ICP alone.

**Brain Tissue Oxygen and Cerebral Perfusion Pressure**

Several studies have examined the relationship between PbtO2 and CPP but have produced conflicting results. Most studies examining the effects of induced hypertension on PbtO2 have demonstrated an increase in PbtO2 in response to augmented CPP. In part, variations of response may reflect differences in the status of pressure autoregulation. In experimental models, PbtO2 shows a close relationship with changes in CBF. Therefore, PbtO2 may have a close relationship with progressive oligemia and warn of impending ischemia.

**Brain Tissue Oxygen and Hemoglobin**

Isovolemic hemodilution reduces brain oxygenation and increases lesion size in TBI under experimental conditions, and PbtO2 decreases after hemorrhagic shock but responds to resuscitation. The avoidance of significant anemia in TBI is warranted. However, the thresholds for transfusion are unclear because transfusion has potential systemic adverse effects, transfused stored blood does not have the same oxygen-carrying capacity as the patient’s blood, and the impact of the change in rheology in the microvasculature is uncertain. Blood transfusion has a variable influence on PbtO2, but prediction of the response based on pre-transfusion variables is elusive.

**Diffusion Barriers to Brain Tissue Oxygen**

Oxygen transport in the tissues occurs by diffusion, which is affected by PaO2. The diffusion distance between O2 in the capillary and the cell is an important factor determining intracellular oxygen tension, so tissue oxygen decreases non-linearly in the extracellular space with increasing distance from the vessel. Diffusion-limited tissue oxygenation in TBI may be as important as perfusion-limited ischemia, but is more difficult to diagnose. In TBI, microvascular factors that may increase the diffusion distance for oxygen include cytotoxic cell swelling, perivascular edema, collapsed capillaries, and arteriovenous shunting. If these factors play a significant role in impairing oxygen diffusion to the cell, the partial pressure of oxygen in the capillary may be of greater significance than in normal physiology.

**Brain Tissue Oxygen and Outcome in Adult Patients**

Several studies have examined the relationship between PbtO2 and outcome after TBI in adult patients. Low PbtO2 occurs most commonly in the first 24 hours after TBI, which is consistent with the lower CBF, increased lactate, and cellular acidosis seen during this period. The risk for poor outcome has been linked with the depth and duration of cerebral hypoxia. Valadka et al. demonstrated that the longer PbtO2 values were below 20mmHg, the greater the likelihood of dying, with the difference between patients alive and dead becoming significant at PbtO2 values less than 6mmHg (the difference gradually widening the lower the threshold became). Two studies have examined PbtO2-monitored patients with historical controls and have suggested that a PbtO2-targeted approach may be of benefit to patients. PbtO2 appears to decrease to zero when brain death occurs.

**Brain Tissue Oxygen Monitoring in Children**

The rationale for using additional monitors to help determine the choice of therapy in children with acute brain injury is arguably stronger than for adults. For example, in adult severe TBI there is considerable debate about what CPP target should be aimed for. Management of CPP in children is further complicated by the changing physiological profiles and normative values with age, in particular those that relate to ICP and blood pressure (BP). Therefore, a marker of the adequacy of BP and ICP control to deliver oxygen to the brain would appear to be of great value. However, there are few papers that have specifically examined PbtO2 monitoring in children. The evidence from these agrees with the adult studies that low PbtO2 is associated with poor outcome. In particular, the longer patients had PbtO2 below 20mmHg, the more likely they were to have a poor outcome, with the key threshold of 10mmHg having the strongest association with outcome. Markers of primary injury severity do not appear to predict which patients are at risk for secondary brain tissue hypoxic injury.

In the largest of these pediatric studies (52 children with severe TBI), low PbtO2 (<10mmHg) was independently associated with poor outcome (mortality and dichotomized outcome parameters using the Glasgow Outcome Score and Pediatric Cerebral Performance Category Score). Furthermore, PbtO2 was the strongest predictor of outcome in multivariate analysis, which included injury severity, Glasgow Coma Scale, and ICP and CPP secondary insults. Mortality in the series was low (9.6%). PbtO2 has a weak correlation with ICP and CPP in pediatric TBI when measured as secondary insults and as time-linked observations in all patients, probably because several factors influence PbtO2, PbtO2 may be low despite normal ICP, and high ICP may occur with normal or even elevated PbtO2 (as may occur with hyperemia). However, in individual children, high ICP may compromise PbtO2, and therapy such as decompressive craniectomy may reduce ICP and improve PbtO2.

Little has been published about PbtO2 monitoring for other pathologies in children. One such study reported the occurrence of a precipitous decline of PbtO2 in patients with tuberculous meningitis despite full treatment with anti-tuberculous medication and steroids, and normalized ICP and BP. At our institution, low PbtO2 was associated with the development of delayed cerebral infarction on head computed tomography (CT) scan in patients with trauma, SAH, cerebral infection, and metabolic encephalopathy (unpublished data).

In summary, studies in children suggest that episodes of low PbtO2 are common in TBI, are not predicted by other conventional monitoring, and are associated with poor outcome. Although mortality in the largest series was low, and historical cohort studies in adults suggest benefit to patients, PbtO2-directed treatment has not been subjected to a randomized trial as yet.

**A Practical Guide to Managing Low Brain Tissue Oxygen—An Institutional Approach**

**Placement of Catheters**

At our institution, a PbtO2 monitor is placed whenever we monitor ICP in patients with acute neurological pathology. The catheter is placed into
right fronto white matter if there are no focal lesions, or in an area close to a lesion or contusion if there is focal pathology. The PbtO$_2$ readings are allowed to settle for one hour before any intervention is planned. FiO$_2$ is increased to test the monitor for an appropriate response to PaO$_2$. A head CT scan is performed when the patient is stable to confirm the location of the catheter tip.

**Treatment of Low Brain Tissue Oxygen**

Our approach to low PbtO$_2$ emphasizes individualization of patient care. The type of injury, profiles of ICP and BP, status of pressure autoregulation, metabolic dysregulation, and systemic injury/disease are but some of the issues that influence decisions in the individual patient. In general terms, we begin with a search for a possible reversible cause for low PbtO$_2$, such as high or borderline ICP, low CPP, low hemoglobin, low PaO$_2$, low PaCO$_2$, subclinical seizures, or cerebral vasospasm. If there is an apparent cause for low PbtO$_2$ that can be identified, we address this first. In the absence of these, we elevate the CPP by 5–10mmHg and observe its effect on PbtO$_2$ and ICP. If PbtO$_2$ improves and ICP is either unchanged or marginally increased, we continue at the higher CPP. If PbtO$_2$ does not improve, artificial elevation of CPP may not be beneficial and only the adverse effects remain. If ICP increases in tandem with the BP increase (as occurs when pressure autoregulation is impaired), a decision is made balancing the risks of higher ICP and low PbtO$_2$ based on the absolute values of each. If hemoglobin is less than 10g/dl, we transfuse the patient to examine the effect of higher hemoglobin on PbtO$_2$. If ICP is controlled, we allow the PaCO$_2$ to be maintained at a higher level in the hope that this will promote cerebral vasodilation. If the above methods are not effective, or as a temporary intervention while other therapies are prepared, we increase the FiO$_2$ to increase the partial pressure of oxygen in the tissues.

**Interpretation of Other Variables**

In addition to the treatment of low PbtO$_2$, we have found the response of PbtO$_2$ helpful to interpret other monitored variables or interventions. For example, high ICP may be due to several factors. If PbtO$_2$ is also high (especially if transcranial Doppler flow velocities are elevated), this suggests the high ICP may be due to hyperemia. In this case, lowering PaCO$_2$ may be a useful strategy, and monitoring PbtO$_2$ may add a degree of safety while doing this. When transcranial Doppler velocities are elevated, PbtO$_2$ may help distinguish between hyperemia and vasospasm. Low PbtO$_2$ in the face of high ICP may be due to the rise in ICP, or both may be caused by a third factor, such as subclinical seizures.