Critical Care and Resuscitation 26 (2024) 204–209

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Review Article

Brain tissue oxygen monitoring in moderate-to-severe traumatic brain injury: Physiological determinants, clinical interventions and current randomised controlled trial evidence

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ARTICLE INFORMATION

Article history:
Received 27 March 2024
Received in revised form
23 May 2024
Accepted 30 May 2024

Keywords:
Surgery
Intensive care
Traumatic brain injury
Trauma care delivery

ABSTRACT

Modern intensive care for moderate-to-severe traumatic brain injury (msTBI) focuses on managing intracranial pressure (ICP) and cerebral perfusion pressure (CPP). This approach lacks robust clinical evidence and often overlooks the impact of hypoxic injuries. Emerging monitoring modalities, particularly those capable of measuring brain tissue oxygen, represent a promising avenue for advanced neuromonitoring. Among these, brain tissue oxygen tension ($PbtO_2$) shows the most promising results. However, there is still a lack of consensus regarding the interpretation of $PbtO_2$ in clinical practice. This review aims to provide an overview of the pathophysiological rationales, monitoring technology, physiological determinants, and recent clinical trial evidence for $PbtO_2$ monitoring in the management of msTBI.

1. Introduction

Traumatic brain injury (TBI) is a major cause of death and disability, with up to 26 million people per year suffering from some form of TBI worldwide.[1] Moderate to severe TBI (msTBI), defined by a presenting Glasgow coma score of <13, is the most serious category of TBI. Morbidity and mortality from msTBI are high, with many patients dying or suffering long term disability as a result of their injuries.[2] The enormous social costs and burden of msTBI are difficult to quantify, but the economic costs of the acute and chronic management of msTBI in Australia translates to approximately $A2 billion per year.[3]

msTBI is a complex pathology characterised by multiple interacting pathophysiological processes which are amplified in the early post injury period. The days immediately following injury are therefore an important window in which optimal clinical management (typically provided in the intensive care unit) can ameliorate the impact of these processes on cerebral tissue.[4] Unfortunately, despite a global research endeavour over multiple decades,[5–9] few meaningful advances in the acute management of msTBI have been made. This lack of progress and the recognition of the fundamental complexity of the disease have led to a re-orientation of TBI research towards the identification and examination of the multiple determinants of outcome,[10,11] re-evaluation of how current msTBI management strategies intersect with these factors[12] and a search for more effective therapies, clinical management strategies[13,14] and research approaches.[15]

Clinical management of msTBI in the intensive care unit (ICU) is typically guided by invasively monitored intracranial pressure (ICP) and cerebral perfusion pressure (CPP). Strong associations exist between raised ICP and patient outcomes,[16] and the physiological rationale for ICP and CPP monitoring is both persuasive and familiar to neurotrauma clinicians. However, robust studies assessing this

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https://doi.org/10.1016/j.ccrj.2024.05.003

practice over several decades have yielded inconsistent and inconclusive results.[17,18] Furthermore, exclusive reliance on ICP and CPP for msTBI management disregards the impact of hypoxic and ischaemic injuries, better measured by other neuromonitoring parameters. One such measure is brain tissue oxygen tension ($PbtO_2$), which offers a continuous means of identifying and treating cerebral hypoxia.[19] This monitoring modality is increasingly used to inform the clinical management of patients with acute brain injuries and is the focus of three large randomised controlled trials of msTBI management, BOOST-3 (target n = 1094),[20] BONANZA (target n = 860) and the recently published OXY-TC trial (n = 318).[21] The intention of this review is to provide an overview of the physiological determinants of $PbtO_2$, the pathophysiological impacts of msTBI on $PbtO_2$ and the evidence underpinning current trials that seek to determine whether $PbtO_2$-informed management can improve outcomes in this highly vulnerable patient group.

1.1. Cerebral oxygen demand and supply

Cerebral tissue represents only 2% of body mass but the high metabolic activity of neuronal tissue demands 20% of the body's oxygen supply.[22] This translates to an average requirement for approximately 50 ml of oxygenated blood per 100 g of tissue per minute; this value is higher in grey matter (80 ml/100 g/min) and lower in white matter (20 ml/100 g/min). Delivery of this volume of oxygenated blood to the brain is dependent on the cardiovascular, respiratory, neuromuscular and haematological systems. In addition, the cerebrovascular system provides fine control of tissue blood supply, responding to fluctuations in systemic blood pressure and local tissue demands that vary rapidly with brain activity. Significant dysfunction of any of these systems, e.g. respiratory failure or loss of cerebral autoregulation, can have a detrimental impact on cerebral oxygenation and may exacerbate the effects of primary brain injuries.[22]

1.2. Ischaemia and hypoxia in msTBI

Ischaemic secondary brain injury following TBI was first identified in histopathological studies of TBI patients;[23] these findings have since been replicated in the modern era of protocolised, goal-directed TBI care.[24] Ischaemia has also been identified in msTBI via PET studies demonstrating increased oxygen extraction fraction (OEF).[25] Tissue ischaemia post msTBI is multi-factorial. Patients may suffer from extra-cranial injuries which result in cardiovascular compromise. Raised intracranial pressure from swelling of contused brain tissue or intra-cranial mass lesions, may result in reduced cerebral perfusion, and disruption of cerebrovascular autoregulation may exacerbate the impact of episodes of hypoperfusion.[16] Brain tissue regions that have been compressed by mass lesions (such as a sub-dural haematoma) demonstrate reduced tissue oxygenation[26] resulting from capillary compression, swelling of astrocytic endfeet, microvascular shunting and pericyte dysfunction.[27]

Contused cerebral tissue is hypoxic[28] and oxygen diffusion will be compromised in the oedematous tissue characteristically associated with contusional injury.[29] MRI imaging studies also show diffusion hypoxia in regions remote from macroscopically injured tissue post-TBI.[30,31] Hypoxia can also result from an imbalance between oxygen provision and local tissue oxygen demands. In addition to ischaemia and hypoxia, microdialysis studies clearly demonstrate glycolytic metabolism (evidenced by increased lactate/pyruvate ratios)[32] in hypoxic and normoxic tissue. This indicates a more generalised failure of cerebral oxidative metabolism, characterised by diffusion limitation, mitochondrial uncoupling and hypermetabolism following msTBI.[33]

1.3. The physiology of brain tissue oxygen monitoring

Multiple methods have been developed to assess cerebral oxygenation including jugular venous oximetry ($SjvO_2$) and near intra-red spectroscopy (NIRS). However, the most widely used method involves placement of monitoring probes into the brain parenchyma to directly measure brain tissue oxygenation ($PbtO_2$). Over the last two decades, there has been increasing use of this technology, both in a research and clinical setting,[20] and recent data reinforce that NIRS is not an adequate substitute for $PbtO_2$ monitoring in msTBI.[34] There are two commercially available $PbtO_2$ monitors in Australia. The Licox® brain tissue oxygen probe (Integra LifeSciences, Princeton, NJ, USA), employs polarographic methods and the Clark principle - where oxygen concentration in the vicinity of the probe is proportional to the measured redox potential (Fig. 1). This process is temperature dependent, and therefore the system is internally calibrated to local temperature. The Neurovent® $PbtO_2$ monitor (Raumedic AG, Helmbrechts, Germany) utilises oxygen-dependent fluorescence quenching to estimate local oxygen concentration. This relies on the concentration of molecular oxygen near the probe being proportional to the reduction in measured fluorescent intensity. Multi-modal monitors that measure $PbtO_2$, ICP and temperature using a single catheter are available (Neurovent-PTO®, Raumedic AG, Helmbrechts, Germany). Experimental $PbtO_2$ values measured with each system, are marginally different, although the clinical significance of this is unknown.[35]

Under normal physiological conditions $PbtO_2$ readings reflect arterial PO_2 (approx. 90 mmHg), venous PO_2 (approx. 30 mmHg) and the relative proliferation of arterial and venous vessels surrounding the probe. Typically, 70% of the cortical vasculature is venous resulting in a normal $PbtO_2$ range of 25–40 mmHg.[36,37] Establishing a definitive ischaemic threshold of $PbtO_2$ is not straightforward due to the highly variable oxygen demands of cerebral tissue and a lack of consensus on a definition of ischaemia that applies to all measurement modalities. $PbtO_2$ values measured alongside positron emission tomography scanning data demonstrate ischaemia (as defined by an Oxygen Extraction Fraction <40%) at 14 mmHg,[38] $SjvO_2$ values < 50% correspond to an ischaemic threshold $PbtO_2$ of 8.5 mmHg[39] and the minimum mitochondrial oxygen tension to support ATP synthesis is 1.5 mmHg – a value that corresponds to a $PbtO_2$ of 15–20 mmHg.[40] Beyond the uncertainties around defining ischaemia, $PbtO_2$ values <5 mmHg are strongly associated with cell death.[41]

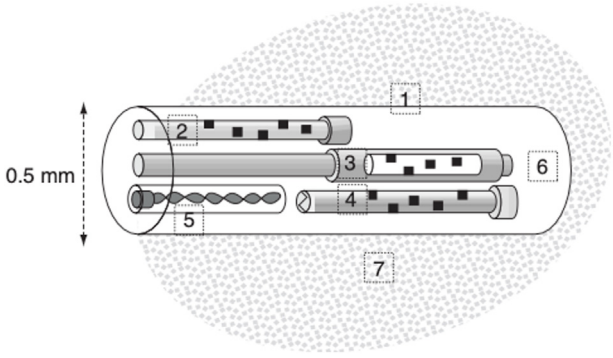

Fig. 1. The Licox® $PbtO_2$ monitor (Integra Lifesciences ltd) combines a Clark electrode with an oxygen sensing length of 7 mm and a thermocouple for internal calibration of oxygen concentration readings to local temperature. 1. Protective covering 2. Gold working electrode 3. Ag/AgCl reference/counter electrode 4. Ionic solution 5. Brain parenchyma. Figure reused with permission.[36]

It is also important to recognise that the burden of cerebral hypoxia is a function of both the depth and duration of the insult. Indeed, in a recently published single-centre cohort of msTBI patients undergoing $PbtO_2$ monitoring, a combined depth and duration analysis suggested $PbtO_2$ values below 25–30 mmHg for 30 min were associated with a transition from favourable to unfavorable outcomes. Similar transitions occurred with shorter durations when the depth of cerebral hypoxia was greater.[42]

1.4. $PbtO_2$ in msTBI

Studies of $PbtO_2$ monitoring in acute msTBI have revealed that brain tissue hypoxia occurs commonly in the setting of protocolised management of ICP and CPP.[43] One study of $PbtO_2$ in msTBI from probes placed in macroscopically normal brain tissue revealed that 30-min episodes of hypoxia occurred frequently: $PbtO_2$ below 15 mmHg occurred in 57% of patients, below 10 mmHg in 42%, and below 5 mmHg in 22%.[44] Two further studies revealed prolonged durations of moderate (15–20 mmHg - median duration 50 min[45]) and severe hypoxia (<15 mmHg – median duration 106 min[46]). There is also evidence that brain tissue hypoxia is strongly associated with both poor neurological outcome and death[44,47,48] and that these risks are exacerbated by concurrent increases in intracranial pressure.[42]

As $PbtO_2$ is a localised measurement, probe placement will strongly influence the reading and how it should be interpreted.[49] The optimal $PbtO_2$ probe insertion location remains uncertain, but it is most commonly placed concurrently with a parenchymal ICP probe, to reduce the need for additional surgical procedures. As such, probes are most commonly positioned in the right frontal lobe, in viable parenchymal brain tissue.[50] However, several studies have demonstrated that $PbtO_2$ readings vary depending on relative probe location, with perilesional measurements appearing to have more prognostic value.[26,49] Positioning such probes can be technically challenging, and as such, prior and currently recruiting trials investigating $PbtO_2$ monitoring in msTBI, have elected to position the probes in the least trauma-affected region of the brain, with the right frontal cortex as the preferred location.[20,21]

Also related to positioning, the depth of probe insertion has been less well studied in comparison to surface location but is conventionally agreed to be approximately 2 cm from the cortical surface, in subcortical white matter.[51] Although clear justification in the literature is lacking, this typically allows for more stable $PbtO_2$ measurement.[52] Critically, regardless of location, the reliability of the probe should be assessed by the response to an 'oxygen challenge', where the $PbtO_2$ response to a temporary increase in the FiO_2 to 1.0 is recorded.[53] Normal probe function is confirmed by an increase in $PbtO_2$ readings of at least 5 mmHg.

1.5. Clinical strategies to increase $PbtO_2$

Brain tissue oxygen is determined by multiple local and systemic factors (Fig. 2). It is therefore possible to influence $PbtO_2$ readings via a variety of clinical interventions. Optimising respiratory parameters and increasing the fraction of inspired oxygen (FiO_2) increases $PbtO_2$ readings by steepening the concentration gradient down which oxygen diffuses into the tissues.[41,54] Augmentation of the cerebral perfusion pressure via inotropic or vasopressor support increases $PbtO_2$[55,56] by increasing both convective transport of oxygen and the surface area for gas exchange.[57] Red blood cell transfusion increases $PbtO_2$ by increasing the oxygen carrying capacity of the blood.[58] Reduction in systemic and cerebral metabolic demand can also be achieved via sedation, neuromuscular blockade and targeted management of seizures and cortical spreading depolarisations. Although each of these strategies can effectively increase $PbtO_2$ readings, computational models reveal significant differences. Increasing FiO_2 can improve tissue oxygenation, however the mechanism of this increase is via the generation of hyperoxia in well perfused tissue. This intervention increases $PbtO_2$ without significantly decreasing the hypoxic tissue fraction and may result in increased oxidative stress. Conversely, increasing cerebral blood flow or haemoglobin concentrations, and decreasing tissue metabolic demand, all resulted in increased $PbtO_2$ and a reduction of hypoxic tissue fraction.[59] These findings are supported by clinical evidence that normobaric hyperoxia does not improve tissue metabolic parameters despite increasing $PbtO_2$ values.[60] Of the available strategies for increasing $PbtO_2$, augmentation of cerebral blood flow via an increase in cerebral perfusion pressure is best supported by theoretical models at the level of the individual vessel[61] and the capillary network level (via a reduction in capillary transit time heterogeneity).[57,62] Given the compressive nature of some cerebral lesions, CPP augmentation may also contribute to recruitment of pathologically compressed capillary beds.[26,62] These theoretical assertions are supported by a growing body of clinical data indicating that maintenance and augmentation of CPP is linked to both preservation of $PbtO_2$[63,64] and improved long term outcome in msTBI.[42]

Scale	Determinants	Effect on oxygen delivery and hypoxic insult	Clinical goal	Clinical interventions
Systemic	Respiratory parameters	PaO_2 affects oxygen association and systemic oxygen content (SaO_2)	Increase SaO_2	Ventilator adjustment (increase in FiO_2 / PEEP)
	Haemoglobin concentration	Systemic oxygen-carrying capacity	Increase [Hb]	Red blood cells transfusion
Regional	Cerebral perfusion	Trans-capillary diffusive oxygen delivery	Increase CPP	Increase ABP (vasopressor, inotropes), decrease ICP (CSF drainage, osmotherapy, decompressive craniectomy)
	Cerebral blood flow	Vascular convective oxygen delivery	Increase CBF	Maintain cerebral autoregulation via CPP management, normocapnia, cardiac output optimisation
Local	Microenvironments	Perivascular Oedema and microvascular collapse can reduce capacity to increase OEF	Reduce brain swelling and oedema	Osmotherapy and fluid balance
	Metabolic demand	Increase the risk of energy failure	Reduce metabolic demands	Sedation, analgesia, temperature control, paralysis, barbiturate coma, seizure management

Fig. 2. Determinants of $PbtO_2$ measurements. Abbreviations: partial pressure of arterial oxygen (PaO_2), saturation of arterial oxygen (SaO_2), fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP), concentration of haemoglobin ([Hb]), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), oxygen extraction fraction (OEF), arterial blood pressure (ABP), intracranial pressure (ICP), cerebral spinal fluid (CSF).

1.6. Interventional studies of $PbtO_2$ in msTBI

The strong associations between low $PbtO_2$ and poor outcomes, and the potential for management strategies to improve cerebral oxygenation have led to several attempts to demonstrate improved outcomes via the optimisation of $PbtO_2$ in msTBI. More specifically, this has led to the development of treatment algorithms that guide clinical interventions.[46] These algorithms are typically applied in combination with ICP monitoring, leading to clinical scenarios where one, both, or neither of these parameters are deranged. As such, optimisation may require sophisticated management strategies (as outlined in trial protocols[20,21]), that apply different interventions simultaneously, and may be challenging to implement in $PbtO_2$ naïve settings. Moreover, the optimal duration of $PbtO_2$ monitoring is unclear, with current trial data typically applying optimisation algorithms over the first 5-days in ICU. Whether $PbtO_2$ values remain reliable beyond this period of time is unknown. Finally, it should also be recognised that there are limited health-economic analyses concerning $PbtO_2$ monitoring, which are urgently needed, given the relative cost of these devices and their consumables.

The largest trials of $PbtO_2$ optimisation in msTBI to date are the brain oxygenation in Severe TBI (BOOST 2) trial[51] and the recently published OXY TC trial.[21] BOOST 2 was a two-arm, single blind prospective randomised controlled trial conducted in the United States. Patients with msTBI and a requirement for invasive neuromonitoring were randomised to ICP monitoring alone or ICP plus $PbtO_2$ monitoring and optimisation. $PbtO_2$ optimisation followed a tiered approach, but did not mandate an order of priority for each manoeuvre. Of note, an increased FiO_2 was used most commonly in response to episodes of cerebral hypoxia, and less ICP based interventions were required overall, in the intervention arm. The primary hypothesis was that this optimisation strategy would reduce the total burden of cerebral hypoxia. Secondary hypotheses related to safety, feasibility, and non-futility. The trial was ceased early by the data monitoring and safety committee due to successful demonstration of the primary outcome after 119 of the planned 182 patients were recruited. The trial was not powered to detect significant differences in clinical outcome, but signals of reduced mortality and improved neurological outcome were observed in the $PbtO_2$ group. This encouraging result led to the design and implementation of two similarly designed and prospectively aligned trials (BOOST 3 and BONANZA-GT) which are currently recruiting with the aim of demonstrating benefits in patient centred outcomes from this management strategy. It is important to note that while the BOOST 3 protocol maintains a pragmatic[20] approach to the order of $PbtO_2$ optimisation manoeuvres, it also highlights the potential for iatrogenic harm from over-use of normobaric hyperoxia.

The recently published OXY TC trial conducted by Payen and colleagues was a multi-centre open label, randomised superiority trial conducted at 25 neurotrauma centres in France.[40] Adult patients with msTBI were randomised to either ICP monitoring alone (single catheter) or combined $PbtO_2$/ICP monitoring (two catheters), which had to commence within 16 h of injury. Protocolised care was provided for the first 5-days in the ICU and mandated a specific order of $PbtO_2$ optimisation strategies that prioritised achievement of a PaO_2 of 100–150 mmHg prior to cardiovascular optimisation. A total of 318 participants were enrolled and the primary outcome (GOSE at six months) was available for 271 patients. The trial found no significant differences in mortality or neurological outcomes between the two groups and a higher incidence of probe insertion complications (4%) in the $PbtO_2$ group. The lack of benefit from $PbtO_2$ guided management is somewhat unexpected given previous signals of benefit from similar (albeit smaller) trials. It should be noted that the confidence interval around the primary outcome was wide (95% CI 0.6–1.7) and that a post-hoc analysis of outcomes for patients with raised ICP (>20 mmHg) on probe insertion revealed significantly improved outcomes in the $PbtO_2$ management group (OR 0.13 95%CI 0.02–0.86, $p = 0.034$). Finally, this finding also highlights that the manner by which $PbtO_2$ is optimised may also be critical, and will require greater scrutiny with larger datasets.

1.7. Conclusions

msTBI is a devastating disease for patients, their families and society. It is well accepted that the development of more effective treatment strategies could significantly reduce morbidity and mortality. Accordingly, the high oxygen demands of cerebral tissue, the high incidence of brain tissue hypoxia and the availability of $PbtO_2$ optimisation strategies indicate that $PbtO_2$ guided management could be central to this broader goal.

Early observational data and the results of the BOOST 2 study were grounds for optimism about the efficacy of $PbtO_2$ guided management. However, the discrepancy between the results of BOOST 2 and OXY TC indicate that cerebral oxygenation optimisation may not be universally beneficial in all subtypes of msTBI, and that the method of $PbtO_2$ augmentation may be a significant determinant of any effect. The reported benefit of $PbtO_2$ monitoring in a sub-group of OXY TC patients, raises the possibility that $PbtO_2$ based management may be of particular use in the setting of raised ICP. It is possible that compressive mass lesions and/or contusional injuries will be more responsive to strategies that result in the recruitment and optimisation of the cerebrovascular microcirculation. The identification of a treatment benefit in a subgroup of msTBI (albeit via post-hoc analysis) also highlights a significant and longstanding issue of research in msTBI – namely that the disease classification is based on a clinical syndrome (i.e. GCS<13) rather than on a distinct pathological sub-type. It is possible that some pathophysiological sub-types of msTBI will be much more likely to respond to $PbtO_2$ strategies and that other subtypes e.g. diffuse axonal injury will be unresponsive and dilute any underlying treatment effect.

Discussion around OXY TC has focused on these issues and those of increased complications associated with $PbtO_2$ probe insertion. There is, however, a consensus in the literature[65,66] that investigating the clinical utility of $PbtO_2$ monitoring in msTBI remains an important pursuit and that this modality may yet play an important role in improving patient outcomes. The results from both BOOST 3, BONANZA-GT and the combined data from these two aligned studies, will add further to the growing body of high-quality evidence concerning $PbtO_2$ monitoring and are eagerly awaited.

CRediT authorship contribution statement

Toby Jeffcote and Kuan-Ying Lu contributed equally to the paper as first authors. This included conceptualisation, data synthesis, and manuscript preparation. The remaining authors contributed equally to manuscript preparation and editing. All authors read and approved the submission.

Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Senior author Andrew Udy is part of the Editorial Board of the journal (Critical Care & Resuscitation). If there are other authors, they declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this article.

Acknowledgments

The authors gratefully acknowledge support from the National Health and Medical Resarch Council of Australia and the Medical Research Future Fund; BONANZA; GNT1156636 & GNT1167706.

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