Brain Tissue Oxygen Monitoring in Neurocritical Care

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Introduction

Avoidance of secondary cerebral hypoxia/ischemia is a mainstay of therapy in neurocritical care. On-line monitoring of brain tissue oxygen tension ($PbtO_2$) enables detection of secondary brain hypoxic/ischemic insults and targeting of therapeutic interventions, such as intracranial pressure (ICP) control, cerebral perfusion pressure (CPP) augmentation, blood transfusion, and ventilation. Emerging evidence shows that compared to standard ICP/CPP management, $PbtO_2$-directed therapy may improve outcomes of selected populations of brain-injured patients. Larger prospective multicenter trials are underway to further evaluate the potential benefit of $PbtO_2$-directed therapy.

In light of recent important advances in this topic, the aim of this review is to summarize the physiology underlying $PbtO_2$ monitoring, its main indications and clinical utility, and the potential benefit of $PbtO_2$-directed therapy on outcome.

The Physiology Underlying $PbtO_2$ Monitoring

Definition

$PbtO_2$ is defined as the partial pressure of oxygen in the interstitial space of the brain and reflects the availability of oxygen for oxidative energy production. $PbtO_2$ represents the balance between oxygen delivery and oxygen consumption, and is influenced by changes in cerebral capillary perfusion.

Technology

The technique involves the insertion of a fine catheter (approximately 0.5 mm in diameter) into the brain parenchyma for the continuous monitoring of $PbtO_2$ at the bedside (**Fig. 1**). Catheters can be inserted through a single or multiple lumen bolt via a burr hole or by tunneling, and can be placed in the operating room or at the beside in the intensive care unit (ICU). Probes are generally placed in the sub-cortical white matter adjacent to an ICP catheter and measure $PbtO_2$ locally, in an area of about 15 – 20 mm^2 around the probe. Two devices for $PbtO_2$ monitoring are available (the Licox® system from Integra and the Neurovent® system from Raumedic), which utilize polarographic Clark-type cell with reversible electrochemical electrodes. Post-insertion non-contrast head computed tomography (CT) confirmation of probe position in the brain parenchyma is important for interpretation of readings. A 'run-in' or equilibration time of up to one hour is

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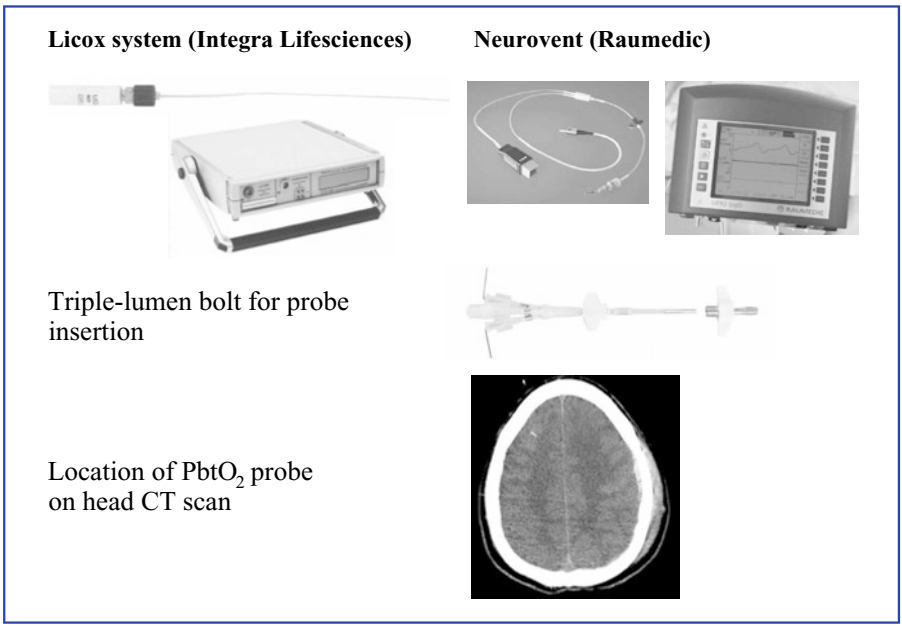

Fig. 1. Figure illustrating the technology underlying brain tissue oxygen tension ($PbtO_2$) monitoring. Insertion of $PbtO_2$ probes into sub-cortical white matter is generally realized via a single or multiple (triple in the example illustrated here) lumen bolt, that can be inserted in the ICU or operating room. Correct catheter placement is controlled with a non-contrast head CT scan. For additional details see text.

required before readings are stable. At the beginning of monitoring, and daily thereafter, an 'oxygen challenge' is performed to evaluate the function and the responsiveness of the $PbtO_2$ probe. The oxygen challenge involves increasing the FiO_2 from baseline to 1.0 for approximately 20 minutes in order to evaluate the probe's responsiveness (defined by an increase of about 2 times of baseline $PbtO_2$). $PbtO_2$ monitoring is safe, causing a small iatrogenic hematoma in less than 2 % of patients, this number comparing favorably with the rate reported with intraparenchymal ICP monitoring, and being much smaller than that associated with external ventricular drains [1]. No catheter-related infections have been reported [2]; technical complication (dislocation or defect) rates may reach 13.6 %, with the greatest $PbtO_2$ display errors measured in the first 4 days [1].

Probe Location

The $PbtO_2$ value is highly dependent on oxygen diffusion from the vasculature to a small amount of tissue [3, 4]. Location of the probe is of critical importance for the interpretation of $PbtO_2$. Most centers have measured $PbtO_2$ in the right 'normal appearing' frontal sub-cortical white matter, particularly in conditions of diffuse brain injury. $PbtO_2$ probes can be placed around focal injuries (e.g., hemorrhagic contusions or hematomas in patients with head trauma, and areas perfused by the artery where the ruptured aneurysm has been secured and are at higher risk of delayed ischemia in patients with subarachnoid hemorrhage

[SAH]). In such areas surrounding brain lesions, $PbtO_2$ values may be lower than those measured in normal appearing tissue [5]. Although considered as regional monitoring, $PbtO_2$ has been shown to be a good indicator of global brain oxygenation, particularly in conditions of diffuse injury [6].

Interpretation of Measured Values

In agreement with recent data indicating that the venous fraction within the cortical microvasculature exceeds 70 %, it is suggested that $PbtO_2$ predominantly reflects venous PO_2 [7]. Among the factors affecting $PbtO_2$, the effects of decreased CPP and cerebral blood flow (CBF) have been studied most [8]. $PbtO_2$ appears to correlate well with regional CBF and the relationship follows the autoregulation curve regulating CBF along a wide range of mean arterial pressures (MAPs) [9]. CPP and MAP augmentation might significantly increase $PbtO_2$ [10] further supporting the notion that $PbtO_2$ can be a good marker of CBF and cerebral ischemia in certain conditions.

$PbtO_2$ is, however, more than a marker of ischemia. Rosenthal and colleagues, using parenchymal thermal diffusion CBF and $PbtO_2$ monitoring, showed that $PbtO_2$ more appropriately reflects the product of CBF and arterio-venous oxygen tension difference ($AVTO_2$) [4]:

$$PbtO_2 = CBF \cdot AVTO_2$$

where $AVTO_2 \approx CaO_2 - CvO_2 \approx [(SaO_2 \cdot 1.34 \cdot [\text{hemoglobin}] + (0.003 \cdot PaO_2)] - [(SvO_2 \cdot 1.34 \cdot [\text{hemoglobin}]) + (0.003 \cdot PvO_2)]$.

The very close association of $PbtO_2$ with the product of CBF and $AVTO_2$ implies a relationship between the amount of dissolved plasma oxygen passing through a given volume of brain per unit time and the steady-state oxygen concentration in brain tissue. Based on the formula $PbtO_2 = CBF \cdot AVTO_2$, reduced $PbtO_2$ occurs frequently because of low CBF. However, PaO_2 is also an important determinant of $PbtO_2$ [11] and additional pathological events (e.g., impaired lung function [12] or reduced oxygen extraction due to increased gradients for oxygen diffusion in injured brain tissue [3]) might decrease $PbtO_2$, in the absence of reduced CBF. $PbtO_2$ is therefore more a marker of cellular function than simply an 'ischemia monitor', which suggests that it may be an appropriate target for therapy.

$PbtO_2$ Thresholds for Therapy

In stable conditions, $PbtO_2$ averages 35 – 50 mmHg, with lower values observed after acute brain injury (25 – 35 mmHg). There has been intense debate about the thresholds for physiologic abnormality that should guide therapeutic interventions (**Table 1**). A $PbtO_2 < 20$ mmHg has been generally accepted as the threshold for compromised brain oxygen or *moderate* brain hypoxia [5, 13, 14]. *Severe* brain hypoxia has been defined as a $PbtO_2 < 10$ mmHg [2]. Recently the Brain Trauma Foundation defined the threshold for *critical* brain hypoxia as a $PbtO_2 < 15$ mmHg, representing the lower threshold to initiate therapy [15]. Trends over time and the duration and the magnitude of brain hypoxia are of outmost importance from the clinical standpoint since they have a great influence on prognosis [2, 13, 14].

Table 1. Physiological and pathological brain tissue oxygen tension ($PbtO_2$) thresholds in humans.

Condition	Values
$PbtO_2$ ranges:	
Neurosurgical patients, stable conditions	35 – 50 mmHg
Neurosurgical patients, acute injury (SAH, TBI)	25 – 35 mmHg
$PbtO_2$ thresholds of brain hypoxia:	
Moderate brain hypoxia (compromised brain oxygen)	20 mmHg
Critical brain hypoxia	15 mmHg*
Severe brain hypoxia	10 mmHg

* $PbtO_2$ threshold to initiate therapy according to Brain Trauma Foundation guidelines (2007).
SAH: subarachnoid hemorrhage; TBI: traumatic brain injury.

Indications for $PbtO_2$ Monitoring

The two major conditions in which $PbtO_2$ monitoring has been applied and might have clinical utility are severe traumatic brain injury (TBI) and poor-grade SAH (**Table 2**).

Table 2. Indications for brain tissue oxygen tension ($PbtO_2$) monitoring

Pathology	Therapeutic interventions that may be targeted to $PbtO_2$
Traumatic brain injury (TBI)	
Severe TBI	*Management of CPP* • Identification of optimal CPP threshold *ICP control* • Evaluate the efficacy of osmotherapy • Aggressive management of ICP (e.g., decompressive craniectomy) if high ICP/low $PbtO_2$ pattern *Blood transfusion* *Lung-protective strategy*
Subarachnoid hemorrhage (SAH)	
Poor grade/ comatose SAH	*Prevention of DCI* • Identify patients at high risk of DCI *Treatment of DCI* • Optimal MAP/CPP threshold for medical therapy of DCI (induced hypertension) *Blood transfusion*

CPP: cerebral perfusion pressure; DCI: delayed cerebral ischemia; ICP: intracranial pressure; MAP: mean arterial pressure

Traumatic Brain Injury

Low $PbtO_2$ is associated with poor outcome after severe TBI [2]. Importantly, it has been demonstrated that secondary brain hypoxic insults may go unnoticed when therapy is guided by ICP/CPP alone and that brain hypoxia can occur despite ICP and CPP being within normal thresholds [13, 14]. Monitoring and management of $PbtO_2$ has been included in international guidelines to complement ICP/CPP guided care of patients with severe TBI [15].

Subarachnoid Hemorrhage

Recent international consensus guidelines have included $PbtO_2$ monitoring as a useful tool to detect delayed cerebral ischemia in comatose/poor-grade SAH patients [16]. In this setting, $PbtO_2$ monitoring might identify patients at high risk for delayed cerebral ischemia [17] and is a valid complement to transcranial Doppler (TCD) and radiographic monitoring. Results from $PbtO_2$ monitoring after SAH also led to questions about the efficacy of triple H therapy in the treatment of delayed cerebral ischemia [18] (see below). In SAH patients, an association between low $PbtO_2$ and outcome has been reported by some [19] but not all [20, 21] authors.

$PbtO_2$-directed therapy

$PbtO_2$ monitoring and management is a good complement to ICP/CPP standard care. Referring to the equation $PbtO_2 = CBF \cdot AVTO_2$ provides valuable information about how to integrate $PbtO_2$ in clinical practice and to direct therapy of brain hypoxia.

Management of Cerebral Perfusion Pressure

The most studied role of $PbtO_2$ in guiding therapy, and possibly the one with greatest clinical utility, is in CPP management. Increased CPP is often associated with increased $PbtO_2$, thereby allowing a CPP threshold to be set to prevent brain hypoxia [10].

The response of $PbtO_2$ to changes in MAP/CPP has been explored in patients with severe TBI [22] and poor-grade SAH [17], in whom the aim was to identify the optimal CPP level above which secondary brain ischemia could be prevented. Interestingly, when using this approach in selected populations of patients with severe TBI, the CPP threshold needed to avoid brain hypoxia was variable (60 – 100 mmHg) across subjects and on average lay between 70 – 75 mmHg, suggesting that optimal CPP may be higher in some TBI patients [23]. Use of $PbtO_2$ monitoring is of value for the continuous surveillance and detection of delayed cerebral ischemia in patients with SAH [17, 20].

In patients with SAH, $PbtO_2$ monitoring has proved helpful to tailor the so-called triple H therapy. Based on evidence showing that the first component of triple H (induced hypertension) improves CBF and $PbtO_2$, whereas the other two components (hemodilution and hypervolemia) have no or even a negative effect on both physiological endpoints [18], induced hypertension alone is now preferred to triple H therapy for the treatment of delayed cerebral ischemia [16].

Control of Intracranial Pressure

Sustained pathological elevations of ICP may translate into reduced CPP and secondary brain hypoxia/ischemia. A recent study showed that when elevated ICP occurs together with low $PbtO_2$, outcome is worse than when ICP is elevated but $PbtO_2$ is normal [14]. Recent studies have shown that $PbtO_2$ monitoring has the potential to improve management of intracranial hypertension. First, the simultaneous occurrence of a pattern of high ICP/low $PbtO_2$ may direct therapy towards

more aggressive management of brain edema, e.g., decompressive craniectomy [24]. Second, recent studies found that hypertonic saline was superior to mannitol in achieving effective and long-lasting reduction of ICP while at the same time improving $PbtO_2$ [25, 26]; thus, $PbtO_2$ may help monitor the efficacy of osmotherapy. Third, since moderate hyperventilation might reduce $PbtO_2$ substantially [27], brain oxygen monitoring can help target optimal $PaCO_2$ during ICP control and prevent further cerebral ischemia.

Additional Interventions

Anemia-induced brain hypoxia has been observed in brain-injured patients and can be corrected by blood transfusion [28, 29]. Monitoring of $PbtO_2$ can thus be used to guide transfusions in patients at risk for brain hypoxia.

Impaired lung function with subsequent reduction in SaO_2, PaO_2 and PaO_2/FiO_2 ratio correlates strongly with brain hypoxia [12]. This argues in favor of lung-protective strategies (positive end-expiratory pressure [PEEP], lung recruitment) guided by $PbtO_2$ in order to improve brain oxygenation and at the same time reduce secondary brain hypoxic insults.

Standardized Algorithm for $PbtO_2$-directed Therapy

A proposed algorithm for $PbtO_2$-directed therapy is illustrated in **Figure 2**. As with all ICU monitoring tools, verification and interpretation of measured values is of outmost importance. Also, despite its potential utility, monitoring of $PbtO_2$ should not be used alone to direct therapy, but rather as part of a multimodal approach. Over-interpretation or aggressive treatment may result in treatment-related complications, which will negate potential outcome benefits [30]. Thus, the importance of monitoring $PbtO_2$ trends over time and examining on-line response to therapeutic trials must be emphasized. For example, in some patients, CPP augmentation [23] or blood transfusion [29] may fail to improve $PbtO_2$, which should then lead to discontinuation of such therapies.

How to treat low $PbtO_2$ is still debated. As for ICP therapy, a stepwise management approach has been proposed, starting when $PbtO_2$ is < 20 mmHg [31]. This strategy includes: (1) give an 'oxygen challenge' (FiO_2 100 % for 2 minutes, to restore $PbtO_2$ temporarily, check functioning of the probe and ensure adequate control of elevated ICP (> 20 mmHg) if necessary; (2) test $PbtO_2$ response to MAP/CPP increase with vasopressors; (3) improve pulmonary function (increase FiO_2 up to 60 %, add PEEP if needed, aspirate pulmonary secretions); (4) reduce excessive metabolic demand (analgesia, sedation, temperature < 37 °C, rule out non-convulsive seizures); (5) administer blood transfusion if hemoglobin concentration is < 9 g/dl. In a recent retrospective study by Bohman and colleagues, the most frequently employed interventions were respiratory manipulations, CPP augmentation and sedation, with an improvement of compromised $PbtO_2$ in about two-thirds of treated episodes and a better outcome in $PbtO_2$ responders [31].

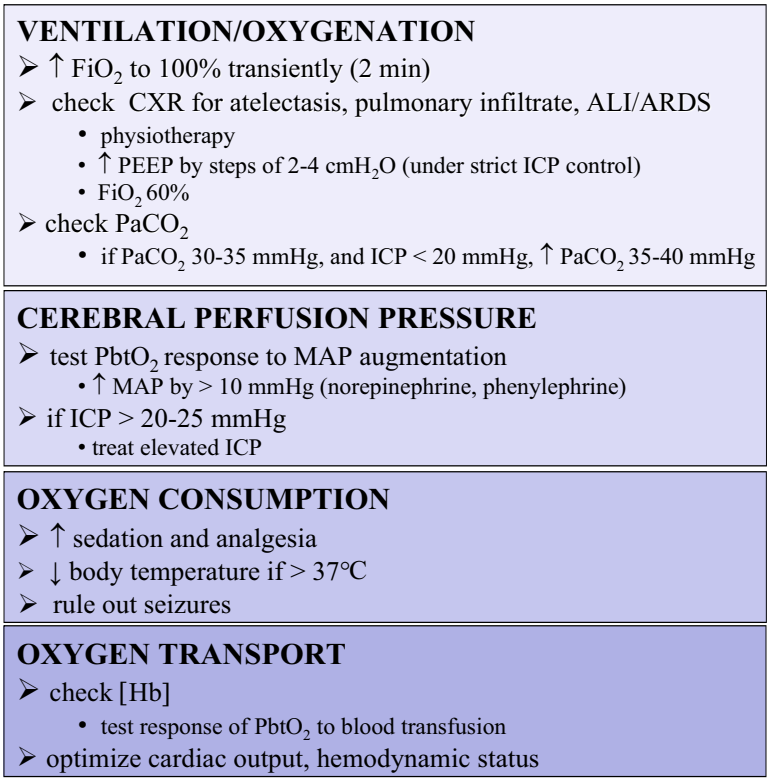

Fig. 2. Stepwise algorithm for brain tissue oxygen tension ($PbtO_2$)-directed therapy (threshold to start therapy: $PbtO_2$ < 15 – 20 mmHg). As with all ICU monitoring tools, verification and interpretation of measured values is of utmost importance. In addition to target thresholds, the importance of monitoring $PbtO_2$ trends over time and carefully evaluating $PbtO_2$ response to therapeutic interventions must be emphasized. Monitoring of $PbtO_2$ should not be used alone to direct therapy, but rather as part of a multimodal approach. CXR: chest x-ray; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICP: intracranial pressure; MAP: mean arterial pressure; Hb: hemoglobin

$PbtO_2$-directed Therapy and Outcome

A large body of evidence shows that reduced $PbtO_2$ is associated with worse outcome after severe TBI [2, 13, 14]. In particular, longer duration of brain hypoxia, irrespective of ICP and CPP levels, is a strong and independent outcome predictor after severe TBI [14]. Given that $PbtO_2$ is an important physiological predictor of outcome it is reasonable to test the hypothesis that $PbtO_2$-directed therapy – aimed to prevent/treat brain hypoxia – might translate into better outcome. This issue has been examined by several studies, all performed in patients with severe TBI, and comparing the effect of $PbtO_2$-directed therapy versus ICP/CPP standard care on patient outcome (**Table 3**). Stiefel and colleagues, in a small retrospective historical control study (n = 53 patients; 27 $PbtO_2$ vs. 26 ICP/CPP therapy), showed that $PbtO_2$-directed therapy (with a threshold of 25 mmHg) reduced mortality from 44 % to 25 % [32]. Meixensberger and colleagues, in a similar histori-

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Table 3. Studies comparing the effect of brain tissue oxygen tension ($PbtO_2$)-directed therapy vs. standard intracranial pressure/cerebral perfusion pressure (ICP/CPP) care on the outcome of patients with severe traumatic brain injury.

First author [ref]	Study type	$PbtO_2$ therapy	ICP/CPP therapy	$PbtO_2$ threshold for therapy	Outcome endpoint	Effect on outcome of $PbtO_2$ vs. ICP/CPP therapy
Meixensberger et al. 2003 [33]	R, historical control	n = 52	n = 39	10 mmHg	6-month GOS	Trend towards better outcome (65 % vs. 54 %, p = 0.27)
Stiefel et al. 2005 [32]	R, historical control	n = 28	n = 25	25 mmHg	Mortality at hospital discharge	Reduced mortality (25 % vs. 44 %, p< 0.05)
Martini et al. 2009 [30]	R, cohort	n = 123	n = 506	20 mmHg	FIM at hospital discharge	Worse outcome (FIM 7.6 ± 3.0 vs. 8.6 ± 2.8, p< 0.01). After adjustment for injury severity, – 0.75 point difference (95 % CI – 1.41 to – 0.09) in mean FIM score with $PbtO_2$ vs. ICP/CPP therapy
McCarthy et al. 2009 [34]	P	n = 63	n = 48	20 mmHg	3-month GOS	Trend towards better outcome (79 % vs. 61 %, p = 0.09)
Narotam et al. 2009 [35]	R, historical control	n = 127	n = 39	20 mmHg	6-month GOS	Better outcome (GOS score 3.55 ± 1.75 vs. 2.71 ± 1.65, p < 0.01; OR of good outcome 2.09, 95 % CI 1.03 – 4.24) Reduced mortality (26 % vs. 41.5 %; RR reduction 37 %)
Spiotta et al. 2010 [36]	R, historical control	n = 70	n = 53	20 mmHg	3-month GOS	Better outcome (64 % vs. 40 %, p = 0.01)

FIM: Functional Independence Measure; GOS: Glasgow Outcome Score; MAP: mean arterial pressure; OR: odds ratio; P: prospective; R: retrospective; RR: relative risk

cal control study (n = 93 patients; 52 $PbtO_2$ vs. 39 ICP/CPP therapy, using a much lower $PbtO_2$ threshold for intervention of 10 mmHg) found that more patients assigned to $PbtO_2$-directed therapy achieved favorable neurological outcome at 6 months than those treated with ICP/CPP care, although this difference was not statistically significant [33]. More recently, four additional studies have measured the benefit of $PbtO_2$-directed therapy in severe TBI patients [30, 34 – 36], and the findings of these studies were conflicting (**Table 3**). McCarthy et al. (n = 145 patients, 81 $PbtO_2$ vs. 64 ICP/CPP therapy) found a trend towards better 6-month outcome with $PbtO_2$-directed therapy ($PbtO_2$ threshold 25 mmHg) versus ICP/CPP care (p = 0.08) [34]. Importantly, although not randomized, this was the only true prospective study. In a historical control study (n = 180 patients; 139 $PbtO_2$

vs. 41 ICP/CPP care, $PbtO_2$ threshold for therapy 20 mmHg), Narotam and colleagues observed similar benefits of $PbtO_2$-directed therapy, in terms of both a significant reduction in mortality rate and a higher proportion of good neurological recovery at 6 months [35]. Similar to their previous study [32], the Philadelphia group more recently reported better 3-month outcome with $PbtO_2$-directed therapy compared to ICP/CPP care [36].

In contrast to these studies however, using a large cohort of 629 severe TBI patients, Martini et al. found worse neurological outcome in the $PbtO_2$-treated group (n = 123 patients, $PbtO_2$ threshold for therapy 20 mmHg) versus the ICP/CPP-treated group (n = 506 patients), and more complications and greater resource consumption [30]. Although patients assigned to $PbtO_2$-directed therapy were more severely injured, these associations remained significant after adjusting for initial cerebral and systemic injury severity, thus questioning the validity and potential outcome benefit of $PbtO_2$-directed therapy. These conflicting results also underline the complexity of such therapy, which furthermore concerns a heterogeneous group of patients, such as those suffering from TBI. In addition, all studies reported until now and summarized in **Table 3** were single-center, most of them (except one [34]) were retrospective historical control or case-matched series, and they used variable $PbtO_2$ thresholds for intervention. Finally, few reported a standardized approach for $PbtO_2$-directed therapy. Given these limitations, a multicenter randomized study comparing $PbtO_2$-directed therapy to ICP/CPP standard care may be of value to test the potential benefit on outcome of this intervention.

Conclusion

The increasing use of $PbtO_2$ monitoring has contributed to ameliorate our understanding of the pathophysiology of acute cerebral conditions, such as TBI and SAH. The integration of $PbtO_2$ as an additional physiological target for therapy has the potential to improve the management of brain-injured patients and to optimize several interventions routinely employed in neurocritical care, such as the management of CPP. As for ICP control, $PbtO_2$-directed therapy is a stepwise multi-interventional approach that needs further standardization and consensus guidelines. Careful management of $PbtO_2$-directed therapy is mandatory to avoid treatment-related complications and to optimize its potential benefit on outcome.

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