Brain Oxygenation Monitoring

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KEYWORDS

- Cerebral oxygenation • Cerebral perfusion • Brain monitoring
- Brain tissue oxygen tension • Jugular venous saturation
- Near-infrared spectroscopy

KEY POINTS

- The maintenance of adequate cerebral oxygenation is a key goal in the management of patients with acute brain injury (ABI) and in certain perioperative settings.
- A mismatch between cerebral oxygen supply and demand can lead to cerebral hypoxia/ischemia and deleterious outcomes; cerebral oxygenation monitoring is, therefore, an important aspect of multimodality neuromonitoring.
- There is abundant evidence of an association between low cerebral oxygenation and outcomes, but limited evidence that increasing cerebral oxygenation improves outcome.
- Advances in cerebral oxygenation monitoring will be driven by improved technology and randomized studies proving the utility of different monitors.

INTRODUCTION

Maintenance of cerebral oxygen supply sufficient to meet metabolic demand is a key goal in the management of patients with ABI and in perioperative settings. A mismatch between oxygen supply and demand can lead to cerebral hypoxia/ischemia and deleterious outcomes, with time-critical windows to prevent or minimize permanent ischemic neurologic injury. The clinical manifestations of cerebral hypoxia/ischemia may remain occult in unconscious or sedated/anesthetized patients, and brain monitoring is required to detect impaired cerebral oxygenation in such circumstances.

Cerebral oxygenation monitoring assesses the balance between cerebral oxygen delivery and utilization, and, therefore, the adequacy of cerebral perfusion and oxygen

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delivery. It can be used to guide treatment to prevent or minimize cerebral hypoxia/ischemia, and is established as an important component of multimodality neuromonitoring in both perioperative and ICU settings.

This article describes the different methods of bedside cerebral oxygenation monitoring, the indications and evidence base for their use, and limitations and future perspectives.

**METHODS OF MONITORING CEREBRAL OXYGENATION**

There exist several imaging and bedside methods of monitoring global and regional cerebral oxygenation, invasively and noninvasively (Table 1). Different monitors describe different physiologic variables and, for this reason, they are not interchangeable.

**Imaging Techniques**

In addition to providing structural information, several imaging techniques are able to evaluate cerebral hemodynamics and metabolism over multiple regions of interest. Imaging provides only a snapshot of cerebral physiology at a particular moment in time and may miss clinically significant episodes of cerebral hypoxia/ischemia, so continuous, bedside monitoring modalities are preferred during clinical management. Readers are referred elsewhere for a detailed description of the role of imaging after ABI.

**Jugular Venous Oxygen Saturation Monitoring**

Jugular venous oxygen saturation monitoring ($SvO_2$) was the first bedside monitor of cerebral oxygenation, but its use is being superseded by other monitoring tools.

<table>
<thead>
<tr>
<th>Bedside monitors of cerebral oxygenation</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>$SvO_2$</td>
<td>Real time</td>
<td>Invasive insertion procedure with risk of hematoma, carotid puncture, and vein thrombosis during prolonged monitoring</td>
</tr>
<tr>
<td></td>
<td>Global trend monitor</td>
<td>Insensitive to regional ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assumes stable CMRO$_2$ to infer CBF changes</td>
</tr>
<tr>
<td>$PtiO_2$</td>
<td>Focal monitor permitting selective monitoring of critically perfused tissue</td>
<td>Focal monitor – the position of the probe is crucial</td>
</tr>
<tr>
<td></td>
<td>Real time</td>
<td>May miss important pathology distant from the monitored site</td>
</tr>
<tr>
<td></td>
<td>The most effective bedside method of detecting cerebral ischemia</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Relatively safe with low hematoma rate (&lt;2%, usually small and clinically insignificant)</td>
<td>Small degree of zero and sensitivity drift</td>
</tr>
<tr>
<td></td>
<td>No reported infections</td>
<td>One-hour run-in period required and thus critical early hypoxic/ischemic episodes may go undetected</td>
</tr>
<tr>
<td>NIRS</td>
<td>Real time</td>
<td>Technical complication rates (dislocation or drift) may reach 13.6%</td>
</tr>
<tr>
<td></td>
<td>High spatial and temporal resolution</td>
<td>Extracerebral circulation may contaminate cerebral oxygenation measurements</td>
</tr>
<tr>
<td></td>
<td>Noninvasive</td>
<td>Lack of standardization between commercial devices</td>
</tr>
<tr>
<td></td>
<td>Assessment of several regions of interest simultaneously</td>
<td>Thresholds for cerebral hypoxia/ischemia undetermined</td>
</tr>
<tr>
<td></td>
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<td>Current devices only monitor relative changes in oxygenation</td>
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</tbody>
</table>
SvO₂ can be measured through intermittent sampling of blood from a catheter with its tip sited in the jugular venous bulb, or continuously using a fiberoptic catheter. SvO₂ represents a global measure of cerebral oxygenation and provides a nonquantitative estimate of the adequacy of cerebral perfusion based on the simple tenet that increased cerebral oxygen demand in the face of inadequate supply increases the proportion of oxygen extracted from hemoglobin and thus reduces the oxygen saturation of blood draining from the brain.² The range of normal SvO₂ values is 55% to 75%, and interpretation of changes is straightforward. Low SvO₂ values may indicate cerebral hypoperfusion secondary to decreased cerebral perfusion pressure (CPP) or hypocapnea, or increased oxygen demand that is not matched by increased supply, whereas high values may indicate relative hyperemia or arteriovenous shunting. The arterial to jugular venous oxygen content concentration difference, and other derived variables, have been studied extensively as an assessment of CBF.³

SjvO₂ monitoring has been used during cardiac surgery and craniotomy, although its primary role is in the neuro-ICU, where it has been used to detect impaired cerebral perfusion after traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), to optimize CPP and, historically, to guide therapeutic hyperventilation. No interventional trials, however, have confirmed a direct benefit of SjvO₂-directed therapy on outcome, and there are several limitations associated with its use (see Table 1). It may miss critical regional ischemia because it is a global, flow-weighted measure. Furthermore, high SjvO₂ values are not necessarily reassuring because they may be associated with pathologic arteriovenous shunting, and brain death.²

Brain Tissue Oxygen Tension Monitoring

Recent years have seen an increasing trend toward the direct measurement of brain tissue partial pressure of oxygen (PtiO₂), particularly in patients in whom intracranial pressure (ICP) monitoring is indicated. PtiO₂ monitoring has the most robust evidence base of all cerebral oxygenation monitors and is now considered the gold standard for monitoring cerebral oxygenation at the bedside.⁴ It has contributed significantly to the understanding of the pathophysiology of ABI and emphasized the importance of multimodality neuromonitoring.⁵

Evidence from studies of patients with TBI demonstrate that cerebral hypoxia/ischemia can occur when ICP and CPP are within established thresholds for normality.⁶ As well as highlighting that ICP and CPP do not directly assess the adequacy of cerebral perfusion, these data suggest that reliance on a single monitoring modality is insufficient to detect cerebral compromise.⁷ PtiO₂ monitoring has also challenged the role of some components of triple-H therapy in the treatment of SAH,⁸ such that induced hypertension alone is now preferred in patients with suspected delayed cerebral ischemia (DCI).

Technical aspects

PtiO₂ catheters are similar in size to intraparenchymal ICP monitors and are placed in subcortical white matter through single or multiple lumen bolts, via a burr hole, or at craniotomy. PtiO₂ readings are unreliable in the first hour after insertion, and a run-in period is essential. This limits intraoperative applications unless the monitor is already in situ. Correct functioning of the probe is confirmed prior to commencing monitoring through an oxygen challenge, which should be repeated on a daily basis thereafter. A normal probe response is an increase of 200% or more from baseline PtiO₂ after an increase in fraction of inspired oxygen (FiO₂) to 1.0 for approximately 20 minutes, although impaired pulmonary function can affect responsiveness.
PtiO$_2$ is a focal measure; the region of interest interrogated by a PtiO$_2$ probe is approximately 17 mm$^2$. Probe placement is, therefore, crucial, and location in at-risk and viable brain tissue is considered optimal by many (Fig. 1). Thus, in patients with focal lesions, such as intracerebral hemorrhage (ICH) or traumatic contusions, a perilesional location is favored, whereas in aneurysmal SAH, probe placement in appropriate vascular territories is advised. Such precise placement can be technically challenging or impossible and risks inadvertent intralesional placement, which does not yield useful information. There is, therefore, an argument for routine PtiO$_2$ probe placement in normal-appearing brain, typically in the nondominant frontal lobe.

Fig. 1. Axial CT scan of the head demonstrating positioning of a PtiO$_2$ probe (arrow) (A) in normal-appearing white matter of the right frontal lobe to measure global cerebral oxygenation; (B) suboptimally within a contusion, which does not yield useful information; and (C) adjacent to a penumbral region to monitor cerebral oxygenation in at-risk tissue. (From Le Roux PD, Oddo M. Parenchymal brain oxygen monitoring in the neurocritical care unit. Neurosurg Clin N Am 2013;24(3):431; with permission.)
when it effectively acts as a global measure of cerebral oxygenation and can guide maintenance of normal physiologic function in uninjured brain. This is the preferred site in cases of diffuse brain injury. Satisfactory probe location must always be confirmed with a nonenhanced cranial CT scan to allow appropriate interpretation of Ptio₂ readings. One major caveat of Ptio₂ monitoring is that heterogeneity of brain oxygenation, even in undamaged areas of brain, is well recognized.⁹

**Indications for brain tissue oxygen tension monitoring**

Ptio₂ monitoring has been used in both ICU and perioperative settings (Table 2), but its primary role, and the one for which there is most evidence, is in the intensive care management of severe TBI.⁶,¹⁰ Recent guidelines from the Neurocritical Care Society recommend that Ptio₂ monitoring can be used to titrate individual targets for CPP, arterial partial pressure of carbon dioxide (Paco₂), arterial partial pressure of oxygen (Pao₂), and hemoglobin concentration, and to manage intracranial hypertension in combination with ICP monitoring.¹¹ The Brain Trauma Foundation recommends monitoring and managing Ptio₂ as a complement to ICP/CPP-guided treatment in patients with severe TBI.¹² It has also been used in poor-grade aneurysmal SAH¹³ and in ICH¹⁴ and has recently been recommended by the Neurocritical Care Society as a means of detecting DCI in sedated or poor-grade SAH patients.¹⁵

There have been several published reports of intraoperative Ptio₂ monitoring but no established role for this indication (see Table 2). A patient with an indwelling Ptio₂ monitor already in place, however, should have monitoring continued during an operative procedure.

**Normal brain tissue oxygen tension values and thresholds for treatment**

Ptio₂ is a complex and dynamic variable representing the interaction between cerebral oxygen delivery and demand⁴ as well as tissue oxygen diffusion gradients.¹⁶ Both cerebral and systemic factors influence Ptio₂ values (Box 1), and Ptio₂ is best considered a biomarker of cellular function as opposed to a simple monitor of hypoxia/ischemia. This makes it an appropriate therapeutic target.

Normal brain Ptio₂ is reported to lie between 20 mm Hg and 35 mm Hg (2.66 kPa and 4.66 kPa). PET studies of patients with TBI suggest that the ischemic threshold is less than 14 mm Hg (<1.86 kPa)¹⁷ and clinical studies indicate that Ptio₂ below 10 mm Hg (<1.33 kPa) should be considered an indicator of severe brain hypoxia.⁹ The threshold for treatment of low Ptio₂ remains, however, undecided, with recommendations for initiation of treatment varying from Ptio₂ less than or equal to 20 mm Hg (<2.66 kPa) to less than or equal to 15 mm Hg (<2 kPa). It is important to appreciate that these thresholds have been determined through patient outcomes in small studies rather than pathophysiologic evidence of ischemic damage at the cellular level.

Crucial to the interpretation of Ptio₂ in the clinical setting is the severity, duration, and chronologic trend of cerebral hypoxia and not absolute Ptio₂ values in isolation, because it is the overall burden of hypoxia/ischemia that is the key determinant of outcome.⁶,⁹ Many uncertainties remain about when and how to treat reduced Ptio₂, and this should be the focus of future research efforts. In particular, the efficacy and safety of increasing FiO₂ to normalize Ptio₂ are uncertain given the (low-quality) evidence of a relationship between arterial hyperoxia and increased mortality after ABI.¹⁸ It also remains to be determined whether Ptio₂ values above a certain threshold ensure adequate cerebral oxygenation or whether or how a mildly elevated ICP should be managed in the presence of normal Ptio₂ values (discussed later).
<table>
<thead>
<tr>
<th>Modality</th>
<th>Indications</th>
<th>Evidence</th>
<th>Highest Quality Evidence</th>
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<tr>
<td>PtiO₂</td>
<td>ICU</td>
<td>Low PtiO₂ is associated with worse mortality, lower GOS, and increased neuropsychological deficits. Treatment of low PtiO₂ may improve outcomes. PtiO₂ can help define individual CPP thresholds. Response to PtiO₂-guided therapy is associated with reduced mortality.</td>
<td>Prospective observational</td>
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<td></td>
<td>Severe TBI</td>
<td>Low PtiO₂ values are associated with increased mortality, but the relationship with morbidity is less clear. PtiO₂-derived ORX autoregulation assessment can predict the risk of DCI and unfavorable outcome. Response to PtiO₂-guided therapy is associated with improved long-term functional outcomes.</td>
<td>Retrospective analysis of prospective observational data</td>
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<tr>
<td></td>
<td>Poor-grade SAH</td>
<td>Low PtiO₂ values are associated with increased mortality, but the relationship with morbidity is less clear. PtiO₂-derived ORX autoregulation assessment can predict the risk of DCI and unfavorable outcome. Response to PtiO₂-guided therapy is associated with improved long-term functional outcomes.</td>
<td>Retrospective analysis of prospective observational data</td>
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<td></td>
<td>ICH</td>
<td>PtiO₂ monitoring may help identify optimal CPP targets. Reduced perihematomal PtiO₂ values are associated with poor outcome. PtiO₂-derived CPP-ORX may predict the development of malignant MCA infarction.</td>
<td>Retrospective</td>
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<tr>
<td></td>
<td>AIS</td>
<td>PtiO₂ monitoring may help identify optimal CPP targets. Reduced perihematomal PtiO₂ values are associated with poor outcome. PtiO₂-derived CPP-ORX may predict the development of malignant MCA infarction.</td>
<td>Retrospective</td>
</tr>
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<td>Perioperative</td>
<td>PtiO₂ values are correlated with severe intracranial angiographic arterial caliber reduction in patients with poor-grade SAH. PtiO₂ threshold of 15 mm Hg is found a sensitive indicator of the likelihood of developing procedure-related ischemia. Correlation is observed between reduced PtiO₂ values and development of a periprobe ischemic infarction.</td>
<td>Case report</td>
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<tr>
<td></td>
<td>Cerebral angiography</td>
<td>Low PtiO₂ values are correlated with severe intracranial angiographic arterial caliber reduction in patients with poor-grade SAH. PtiO₂ threshold of 15 mm Hg is found a sensitive indicator of the likelihood of developing procedure-related ischemia. Correlation is observed between reduced PtiO₂ values and development of a periprobe ischemic infarction.</td>
<td>Case report</td>
</tr>
<tr>
<td></td>
<td>Aneurysm surgery</td>
<td>Low PtiO₂ values are correlated with severe intracranial angiographic arterial caliber reduction in patients with poor-grade SAH. PtiO₂ threshold of 15 mm Hg is found a sensitive indicator of the likelihood of developing procedure-related ischemia. Correlation is observed between reduced PtiO₂ values and development of a periprobe ischemic infarction.</td>
<td>Case report</td>
</tr>
<tr>
<td></td>
<td>AVM surgery</td>
<td>Low PtiO₂ values are correlated with severe intracranial angiographic arterial caliber reduction in patients with poor-grade SAH. PtiO₂ threshold of 15 mm Hg is found a sensitive indicator of the likelihood of developing procedure-related ischemia. Correlation is observed between reduced PtiO₂ values and development of a periprobe ischemic infarction.</td>
<td>Case report</td>
</tr>
<tr>
<td>NIRS</td>
<td>ICU</td>
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<tr>
<td>TBI</td>
<td>There is an association between increasing length of time with $rScO_2 \leq 60%$ and mortality, intracranial hypertension, and compromised CPP.</td>
<td>Prospective observational</td>
<td></td>
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<tr>
<td>SAH</td>
<td>Time-resolved NIRS was able to predict angiographic-proved vasospasm with 100% sensitivity and 85.7% specificity and confirm vasospasm when TCD was not diagnostic.</td>
<td>Prospective observational</td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td>May help predict cerebral edema in patients with complete MCA infarction.</td>
<td>Prospective observational</td>
<td></td>
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<tr>
<td></td>
<td>$rScO_2$ predicts poor outcome during endovascular therapy for AIS.</td>
<td>Prospective observational</td>
<td></td>
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</tbody>
</table>

| Perioperative |
| Carotid surgery | Intraoperative cerebral desaturations may be associated with more major organ morbidity and mortality. | Randomized controlled trial |
|                 | The role of intraoperative cerebral desaturations in postoperative cognitive decline is unclear. | Randomized controlled trial |
|                 | Intraoperative cerebral desaturations may be associated with protracted ICU and hospital LOS, although other authors disagree. | Randomized controlled trial |
| Carotid surgery | There are similar accuracy and reproducibility in the detection of cerebral ischemia compared with TCD and stump pressure. | Prospective observational |
| Head-up (beach chair) position surgery | Hypotension-associated decreases in $rScO_2$ are not associated with a higher incidence of postoperative cognitive dysfunction or serum biomarkers of brain injury. | Prospective observational |

**Abbreviations:** AIS, acute ischemic stroke; AVM, arteriovenous malformation; GOS, Glasgow Outcome Scale score; LOS, length of stay; MCA, middle cerebral artery; ORx, oxygen reactivity index; TCD, transcranial Doppler.
There is currently no consensus on how low \( P_{\text{tiO}_2} \) should be treated. A stepwise approach has been recommended in a manner akin to the treatment of raised ICP, incorporating knowledge of the factors that influence \( P_{\text{tiO}_2} \) values (Fig. 2). Exactly which intervention, or combination of interventions, is most effective in improving \( P_{\text{tiO}_2} \) remains unclear. It seems that it is the responsiveness of the hypoxic brain to a given intervention that is the prognostic factor, with reversal of hypoxia associated with reduced mortality.\(^{19}\)

### Evidence for brain tissue oxygen tension–guided therapy on outcomes

There is a substantial body of evidence corroborating the relationship between low \( P_{\text{tiO}_2} \) values and adverse outcomes after TBI and SAH, but little for other conditions. Furthermore, although there is evidence that interventions, such as CPP augmentation, normobaric hyperoxia, and red blood cell transfusions, can improve low \( P_{\text{tiO}_2} \) values after ABI, robust evidence that this translates into improved outcomes is lacking. In TBI, most outcome-based studies of \( P_{\text{tiO}_2} \)-guided therapy have compared standard ICP/CPP-guided therapy with \( P_{\text{tiO}_2} \)-guided therapy in association with ICP/CPP-guided therapy, with conflicting findings (Table 3). Such variations in reported outcomes may be the result of heterogeneity in study design, including different patient populations, different thresholds for intervention, and the interventions used to treat low \( P_{\text{tiO}_2} \) as well as variable study endpoints. Despite difficulties in controlling for these variations, a systematic review of 4 studies incorporating 491 patients found overall outcome benefits from \( P_{\text{tiO}_2} \)-directed therapy compared with ICP/CPP-guided therapy alone (odds ratio of favorable outcome = 2.1; 95% CI, 1.4 –3.1).\(^{10}\) All studies included in this systematic review, however, were nonrandomized, and only 2 (with small sample sizes) were truly prospective.

Preliminary results have recently been released from a prospective, phase II randomized controlled brain tissue oxygen in TBI (Brain Tissue Oxygen Monitoring in

### Box 1

**The main variables known to influence brain tissue oxygen tension values**

**Systemic variables**
- \( P_{\text{aO}_2} \)
- \( P_{\text{aCO}_2} \)
- \( P_{\text{FiO}_2} \)
- Mean arterial blood pressure
- Cardiopulmonary function
- Hemoglobin level

**Brain-specific variables**
- CPP and ICP
- CBF
- Cerebral vasospasm
- Cerebral autoregulatory status
- Brain tissue gradients for oxygen diffusion
- Composition of the microvasculature around the probe and the relative dominance of arterial or venous vessels

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*Kirkman & Smith*
Fig. 2. Schematic for the management of low Ptio₂ values. EEG, electroencephalography; ETco₂, end-tidal carbon dioxide; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Brain Tissue Oxygen Tension–Guided Therapy, n</th>
<th>Intracranial Pressure/Cerebral Perfusion Pressure–Guided Therapy, n</th>
<th>Brain Tissue Oxygen Tension Threshold for Intervention</th>
<th>Endpoint(s)</th>
<th>Principal Findings</th>
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</thead>
<tbody>
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<td>Adamides et al, 62 2009</td>
<td>Prospective</td>
<td>20</td>
<td>10</td>
<td>2.66 kPa (20 mm Hg)</td>
<td>GOS at 6 months</td>
<td>No significant difference in mean GOS score between the 2 groups (PtiO₂ group = 3.55, ICP/CPP group = 4.40; P = .19)</td>
</tr>
<tr>
<td>Meixensberger et al, 63 2003</td>
<td>Retrospective (historical controls)</td>
<td>53</td>
<td>40</td>
<td>1.33 kPa (10 mm Hg)</td>
<td>GOS at 6 months</td>
<td>A nonsignificant trend toward improved outcomes in the PtiO₂ group (GOS score of 4 or 5 in PtiO₂ group = 65%, in ICP/CPP group = 54%; P = .27)</td>
</tr>
<tr>
<td>Stiefel et al, 64 2005</td>
<td>Retrospective (historical controls)</td>
<td>28</td>
<td>25</td>
<td>3.33 kPa (25 mm Hg)</td>
<td>In-hospital mortality</td>
<td>Mortality rate in PtiO₂ group (25%) significantly lower than ICP/CPP group (44%; P&lt;.05)</td>
</tr>
</tbody>
</table>
| Martini et al, 65 2009 | Retrospective cohort study  | 123                                            | 506                                                                | 2.66 kPa (20 mm Hg)                                 | In-hospital mortality, FIM at hospital discharge | Slightly worse adjusted mortality in PtiO₂ group compared with ICP/CPP group (adjusted mortality difference 4.4%, 95% CI, –3.9%–13%) 
Worse functional outcomes at discharge in the PtiO₂ group (adjusted FIM score difference –0.75; 95% CI, –1.41 to –0.09) |
<p>| McCarthy et al, 66 2009 | Prospective                | 81                                             | 64                                                                  | 2.66 kPa (20 mm Hg)                                 | In-hospital mortality, GOS every 3 mo postdischarge | No significant difference in mortality rates between PtiO₂ group (31%) and ICP/CPP group (36%; P = .52). A nonsignificant trend toward improved outcome (GOS score of 4 or 5) in PtiO₂ group (79%) compared with ICP/CPP group (61%; P = .09). |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Mean PtiO₂ (mm Hg)</th>
<th>Outcome Measure</th>
<th>Summary</th>
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<tbody>
<tr>
<td>Narotam et al, 2009</td>
<td>Retrospective (historical controls)</td>
<td>139</td>
<td>2.66 kPa (20 mm Hg)</td>
<td>GOS at 6 mo</td>
<td>Higher mean GOS score in PtiO₂ group (3.55 ± 1.75) compared with ICP/CPP group (2.71 ± 1.65; P&lt;.01). OR for good outcome in PtiO₂ group = 2.09 (95% CI, 1.03–4.24). Reduced mortality rate in the PtiO₂ group (26% vs 41.5%; RR reduction 37%) despite higher ISS scores in PtiO₂ group</td>
</tr>
<tr>
<td>Spiotta et al, 2010</td>
<td>Retrospective (historical controls)</td>
<td>70</td>
<td>2.66 kPa (20 mm Hg)</td>
<td>In-hospital mortality, GCS at 3 months</td>
<td>Mortality rates significantly lower in PtiO₂ group (26%) than ICP/CPP group (45%; P&lt;.05). A favorable outcome (GOS score of 4 or 5) was also observed more commonly in the PtiO₂ group (64% vs 40%; P = .01).</td>
</tr>
<tr>
<td>Green et al, 2013</td>
<td>Retrospective cohort study</td>
<td>37</td>
<td>2.66 kPa (20 mm Hg)</td>
<td>In-hospital mortality, GOS and FIM at discharge</td>
<td>No survival difference offered by PtiO₂-guided therapy (64.9% vs 54.1%, P = .34) or difference in discharge GCS or FIM. Of note, the PtiO₂-guided therapy group had significantly lower ISS at baseline.</td>
</tr>
<tr>
<td>Shutter, 2014</td>
<td>Prospective phase II RCT</td>
<td>53</td>
<td>2.66 kPa (20 mm Hg)</td>
<td>Proportion of time PtiO₂ &lt;20 mm Hg</td>
<td>Median proportion of time with PtiO₂ &lt;20 mm Hg significantly lower in the ICP/PtiO₂ group (0.14) compared with the ICP group (0.44, P&lt;.00001). No significant difference between adverse events, and protocol violations were infrequent. Lower overall mortality and poor outcome on the 6-mo GOS-extended in the ICP/PtiO₂ group, but neither reached statistical significance (P = .229 and P = .221, respectively).</td>
</tr>
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</table>

**Abbreviations:** FIM, functional independence measure; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score; ISS, injury severity score; LOS, length of stay; MAP, mean arterial pressure; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.
Traumatic Brain Injury [BOOST]-2) trial, which evaluated the safety and efficacy of PtiO₂-directed therapy in 110 adult patients with nonpenetrating severe TBI. Participants were randomized to receive either treatment based on ICP monitoring and management alone (target ICP <20 mm Hg) or treatment based on ICP (same target ICP) and PtiO₂ monitoring based on a prespecified protocol to maintain PtiO₂ greater than 20 mm Hg. The time spent with PtiO₂ less than 20 mm Hg was significantly lower in those in the ICP/PtiO₂ group, and there was no difference in adverse events between the 2 treatment arms. There was a trend toward lower overall mortality and less poor outcome in the ICP/PtiO₂ group, although these differences were not statistically significant (P = .229 and P = .221, respectively), which is unsurprising because this study was not powered for outcome. A larger phase III trial is required to clarify the potential outcome benefits of PtiO₂-guided therapy in TBI as well as in other brain injury types.

**Near-infrared Spectroscopy**

Near-infrared spectroscopy (NIRS)-derived cerebral oximetry is currently the only noninvasive, bedside monitor of cerebral oxygenation. Commercial devices measure regional cerebral oxygen saturation (rScO₂) with high temporal and spatial resolution and permit simultaneous measurement over multiple regions of interest. Despite interest in the clinical application of NIRS for more than 3 decades, widespread translation into routine clinical practice has not occurred.

**Technical aspects**

Full technical details of the principles of NIRS are beyond the scope of this review, and for further information readers are referred elsewhere. In brief, NIRS systems are based on the transmission and absorption of near-infrared (NIR) light (wavelength range 700–950 nm) as it passes through tissue. Several biological molecules, termed chromophores, have distinct absorption spectra in the NIR, and their concentrations can be determined by their relative absorption of light in this wavelength range. From a clinical perspective, oxyhemoglobin and deoxyhemoglobin are the most commonly measured chromophores, although cytochrome-c oxidase (CCO), the terminal complex of the electron transfer chain, is increasingly investigated as a marker of cellular metabolism and may prove clinically more relevant. In adults, NIR light cannot pass across the whole head so the light source and detecting devices are located a few centimeters apart on the same side of the head (reflectance spectroscopy), allowing examination of the superficial cortex.

NIRS interrogates arterial, venous, and capillary blood within the field of view, so rScO₂ values represent a weighted tissue oxygen saturation measured from these 3 compartments. rScO₂ values are also influenced by several physiologic variables, including arterial oxygen saturation, Paco₂, systemic blood pressure, hematocrit, cerebral blood flow (CBF), cerebral blood volume, cerebral metabolic rate for oxygen (CMO₂), and cerebral arterial:venous (a:v) ratio.

Most commercial devices use spatially resolved spectroscopy to derive a scaled absolute hemoglobin concentration representing the relative proportions of oxyhemoglobin and deoxyhemoglobin within the field of view, from which rScO₂ is calculated and displayed as a percentage value. Frequency (or domain)-resolved spectroscopy and time-resolved spectroscopy allow measurement of absolute chromophore concentration with obvious advantages. More recently, diffuse correlation spectroscopy techniques have been developed to monitor CBF and derive CMRO₂.

There are several concerns over the clinical application of NIRS, in particular contamination of the signal by extracranial tissue. Some commercial cerebral oximeters use 2 detectors and a subtraction-based algorithm to deal with this problem,
assuming that the detector closest to the emitter receives light that has passed mainly through the scalp and that the farthest light has passed mainly through brain tissue. Although there is weighting in favor of intracerebral tissue with an emitter-detector spacing greater than 4 cm, even spatially resolved spectroscopy is prone to some degree of extracerebral contamination, and this is particularly problematic during low CBF states. The NIRS-derived CCO signal is highly specific for intracerebral changes, potentially making it a superior biomarker to hemoglobin-based NIRS variables.

**Indications**

There are many Food and Drug Administration–approved NIRS devices available for clinical use. Because the specific algorithms incorporated into commercial devices vary, and are often unpublished, it is difficult to compare rScO₂ values between devices and, therefore, between studies using different devices. There are few numbers of high-quality clinical studies to guide the clinical use of NIRS, and prospective randomized studies are required not only to establish its potential role in patient monitoring but also to assess the relative efficacy of the multitude of devices on the market.

Recent years have seen a significant increase in the use of perioperative cerebral oximetry (see Table 2), particularly during cardiac and carotid surgery, and surgery in the head-up (beach chair) position. Although secondary ischemic injury after ABI is common, and low rScO₂ values have been associated with poor outcome in case series, data on the use of NIRS in the ICU management of ABI are limited and no outcome studies of NIRS-guided treatment have been published.

There are emerging applications for NIRS as a noninvasive monitor of cerebral autoregulation, using standard signal processing techniques and also novel analytical techniques of multimodal monitoring of slow-wave oscillations. NIRS has also been used to determine optimal CPP noninvasively in patients with TBI. Because of the key role of CCO in mitochondrial metabolism, monitoring CCO concentration in addition to oxygenation variables may aid in the determination of ischemic thresholds after ABI by providing additional information about cellular metabolic status.

One challenge in the application of NIRS after ABI is that the presence of intracranial hematoma, cerebral edema, or subarachnoid blood may invalidate some of the assumptions on which NIRS algorithms are based. This has been used to advantage in the identification of intracranial hematomas and cerebral edema.

**Normal regional cerebral oxygen saturation values and thresholds for treatment**

The normal range of rScO₂ is usually reported to lie between 60% and 75%, but there is substantial intraindividual and interindividual variability; NIRS-based cerebral oximetry is, therefore, best considered as a trend monitor. There are no validated rScO₂-derived ischemic thresholds, but clinical studies and management protocols often use absolute rScO₂ values of less than or equal to 50% or a greater than or equal to 20% reduction from baseline as a trigger for initiating measures to improve cerebral oxygenation.

**Evidence of near-infrared spectroscopy–guided therapy on outcomes**

The only evidence for outcome effects of NIRS-guided treatment is from 3 randomized controlled trials in patients undergoing cardiac surgery (Table 4). In small studies, intraoperative cerebral oxygen desaturation has been associated with early and late cognitive decline after cardiac surgery, but a recent systematic review concluded that only low-level evidence links intraoperative desaturation with postoperative neurologic complications. There is also insufficient evidence to conclude that interventions to prevent or treat reductions in rScO₂ are effective in preventing stroke or postoperative cognitive dysfunction after cardiac surgery. NIRS-guided therapy may...
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Abbreviations: CABG, coronary artery bypass grafting; LOS, length of stay; OR, odds ratio.

- **a** Major organ morbidity and mortality (MOMM) composed of the following variables as determined by the Society of Thoracic Surgeons: death, stroke, reoperation for bleeding, mediastinitis, surgical reintervention, renal failure requiring dialysis, and ventilation time greater than 48 hours.
- **b** Desaturation score calculated by multiplying $r\text{Sc}{O}_2$ less than 50% by duration in seconds.
- **c** High-risk cardiac surgery defined by the authors as redo surgery, adult congenital surgery, thoracic aortic surgery with and without circulatory arrest, and combined procedures surgery.
improve overall organ outcome after cardiac surgery, suggesting a role for NIRS as a monitor of overall organ perfusion. A systematic review of the role of rScO₂ in pediatric patients undergoing surgery for congenital heart disease also concluded that there is no evidence that rScO₂ monitoring and management lead to a clinical improvement in short-term neurologic outcome in this patient population.

Several methods are used to assess the adequacy of CBF and oxygen delivery during carotid surgery to inform the critical decision regarding shunt placement during the vessel cross-clamp period. Cerebral oximetry has similar accuracy for the detection of cerebral ischemia compared with other commonly used monitoring modalities and has advantages in terms of simplicity. Various thresholds have been used to determine the need for shunt placement, ranging from a 10% to 20% reduction in ipsilateral rScO₂ from baseline. Cerebral oximetry has higher temporal and spatial resolution compared with other modalities and thus may find a role in guiding the manipulation of systemic physiology to minimize the risk of cerebral hypoxia/ischemia during carotid surgery. Recently, the use of a time-resolved optical imaging system, which allows simultaneous acquisition of data from 32 regions of interest over both hemispheres, has been described. Distinct patterns of changes in hemoglobin and oxyhemoglobin were observed in ipsilateral brain cortex, suggesting that noninvasive optical imaging of brain tissue hemodynamics may find a role during carotid surgery.

There has been intense interest in the application of cerebral oximetry in patients undergoing surgery in the beach chair position because of the risk of hypotension-related cerebral ischemic events in anesthetized patients in the steep head-up position. In a recent study of 50 patients undergoing shoulder surgery in the beach chair position, the incidence of intraoperative cerebral desaturation events (defined as decreases in rScO₂ of ≥20% from baseline) was 18%. Of those experiencing desaturation, the mean maximal decrease in rScO₂ was 32% from preoperative baseline, and the mean number of separate desaturation events was 1.89 with an average duration of more than 3 minutes. Despite this apparently alarming high burden of cerebral desaturation, these authors and other investigators have not identified an association between desaturation events and postoperative neurocognitive dysfunction in this patient population. It has been suggested that changes in intracranial geometry and cerebral a:v ratio related to movement from supine to upright position might account, at least in part, for the changes in measured cerebral saturations.

Finally, there is no evidence that monitoring and early detection of cerebral desaturations to guide targeted interventions improves perioperative outcomes during other surgical procedures under general anesthesia.

FUTURE PERSPECTIVES

Technological developments are likely to be key drivers in advancing cerebral oxygenation monitoring and its adoption in the ICU and perioperative settings. A multiparameter probe that combines ICP, PtiO₂, and temperature measurements is available commercially (Raumedic, Münchenberg, Germany), allowing multimodality monitoring via a single invasive device. The addition of CBF quantification into such a probe is likely. Advances in PtiO₂ technology should allow for improved insertion techniques and more durable devices, and stereotactic placement of invasive probes may help target regions of interest with improved accuracy.

Cerebral arterial oxygen saturation has been estimated using fiberoptic pulse oximetry, and a prototype invasive probe that combines NIRS and indocyanine green dye dilution has been investigated for the simultaneous monitoring of ICP,
CBF, and cerebral blood volume, avoiding NIRS signal contamination by extracerebral tissues. Combined NIRS/electroencephalography provides a unique opportunity to acquire, noninvasively and simultaneously, regional cerebral electrophysiologic and hemodynamic data to elucidate on neurovascular coupling mechanisms. A prototype device combining diffuse correlation spectroscopy and NIRS for the bedside measurement of CBF and cerebral oxygenation respectively has been described. In the future, a single NIRS-based device may be able to provide noninvasive monitoring of cerebral oxygenation, hemodynamics, and cellular metabolic status over multiple regions of interest, although substantial technological advances are necessary before any of these techniques can be introduced into routine clinical practice.

SUMMARY

Cerebral oxygenation represents the balance between cerebral oxygen supply and demand, and a mismatch may lead to cerebral hypoxia/ischemia with deleterious outcomes. There are several tools available for the detection of cerebral hypoxia/ischemia, each with inherent advantages and disadvantages. Although there is a large body of evidence supporting an association between cerebral hypoxia/ischemia and poor outcomes, it remains to be determined whether restoring cerebral oxygenation improves outcomes. The adoption of a multimodality neuromonitoring approach (see Kirkman MA, Smith M: Multimodality Neuromonitoring, in this issue) that incorporates cerebral oxygenation monitoring in addition to more established ICP and CPP monitoring is required, along with large randomized prospective studies to address the current uncertainties about such approaches.

REFERENCES


