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Brain Oxygenation Monitoring

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Key words: 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 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.

Article synopsis:

A mismatch between cerebral oxygen supply and demand can lead to cerebral hypoxia/ischemia and deleterious outcomes. Cerebral oxygenation monitoring is an important aspect of multimodality neuromonitoring in both the perioperative and intensive care unit settings. It is increasingly deployed whenever ICP monitoring is indicated. Although there is a large body of evidence demonstrating an association between cerebral hypoxia/ischemia and poor outcomes, it remains to be determined whether restoring cerebral oxygenation leads to improved outcomes. Randomized prospective studies are required to address the current uncertainties about cerebral oxygenation monitoring and management. This chapter will describe the different methods of monitoring cerebral oxygenation, their indications, evidence base, limitations and future perspectives.

INTRODUCTION

Maintenance of cerebral oxygen supply sufficient to meet demand is a key goal in the management of patients with acute brain injury (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 neurological 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 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 intensive care unit (ICU) settings.

This chapter will describe the different methods of bedside cerebral oxygenation monitoring, the indications and evidence base for their use, as well as limitations and future perspectives.

METHODS OF MONITORING CEREBRAL OXYGENATION

There exists several imaging and bedside methods of monitoring global and regional cerebral oxygenation, invasively and non-invasively (table 1). Different monitors describe different physiological variables and, for this reason, they are not interchangeable.

Table 1 near here

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.

The reader is referred elsewhere for a detailed description of the role of imaging after ABI [1].

Jugular venous oxygen saturation monitoring

Jugular venous oxygen saturation monitoring ($S_{vj}O_2$) was the first bedside monitor of cerebral oxygenation, but its’ use is being superseded by other monitoring tools.

$S_{vj}O_2$ can be measured through intermittent sampling of blood from a catheter with its tip sited in the jugular venous bulb, or continuously using a fiber-optic catheter.

$S_{vj}O_2$ represents a global measure of cerebral oxygenation and provides a non-quantitative 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 $S_{vj}O_2$ values is 55% to 75%, and interpretation of changes is relatively straightforward. Low $S_{vj}O_2$ 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 hyperaemia 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].

$S_{jv}O_2$ monitoring has been used during cardiac surgery and craniotomy, although its primary role is in the neurointensive care unit where it has been used to detect impaired cerebral perfusion after traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), to optimize CPP and, historically, guide therapeutic hyperventilation. However, no interventional trials have confirmed a direct benefit of $S_{jv}O_2$ -directed therapy on outcome, and there are several limitations associated with its use (table 1). Importantly, it may miss critical regional ischemia because it is a global, flow-weighted measure. Further, high $S_{jv}O_2$ values are not necessarily reassuring as they may be associated with pathological arteriovenous shunting, and brain death [2].

Brain tissue oxygen tension monitoring

Recent years have seen an increasing trend towards the direct measurement of brain tissue PO_2 ($P_{ti}O_2$), particularly in patients in whom 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 our 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 intracranial pressure (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 sub-cortical white matter through single or multiple lumen bolts, via a burr-hole, or at craniotomy. PtiO₂ readings are unreliable in the first hour following 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 following an increase in FiO₂ to 1.0 for approximately 20 minutes, although impaired pulmonary function can affect responsiveness.

PtiO₂ is a focal measure; the region of interest interrogated by a PtiO₂ probe is approximately 17 mm². Probe placement is therefore crucial (figure 1), and location in ‘at risk’ and viable brain tissue is considered optimal by many. Thus, in patients with focal lesions such as intracerebral hemorrhage (ICH) or traumatic contusions, a peri-lesional location is favored, whilst 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 PtiO₂ probe placement in ‘normal appearing’ brain, typically in the non-dominant frontal lobe, when it effectively acts as a global measure of cerebral oxygenation and can guide maintenance of normal physiological function in uninjured brain. This is the preferred site in cases of diffuse brain injury. Satisfactory probe location must always be confirmed with a non-enhanced cranial computed tomography (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].

Figure 1 near here

Indications for PtiO₂ 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 of

CPP, PaCO₂, 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 SAH [13], in ICH [14], and has recently been recommended by the Neurocritical Care Society as a mean of detecting DCI in sedated or poor grade SAH patients [15].

Table 2 near here

There have been several published reports of intraoperative PtiO₂ monitoring, but no established role for this indication (table 2). However, a patient with an indwelling PtiO₂ monitor already in place should have monitoring continued during an operative procedure.

Normal PtiO₂ values and thresholds for treatment

PtiO₂ is a complex and dynamic variable representing the interaction between cerebral oxygen delivery and demand [4], as well as tissue oxygen diffusion gradients [16]. Both cerebral and systemic factors influence PtiO₂ values (table 3), 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.

Table 3 near here

Normal brain PtiO₂ is reported to lie between 20 and 35 mmHg (2.66 and 4.66 kPa). Positron emission tomography studies of patients with TBI suggest that the ischemic threshold is less than 14 mmHg (< 1.86 kPa) [17], and clinical studies indicate that PtiO₂ below 10 mmHg (< 1.33 kPa) should be considered an indicator of severe brain hypoxia [9]. However, the threshold for treatment of low PtiO₂ remains undecided with recommendations for initiation of treatment varying from PtiO₂ ≤ 20 mmHg (≤ 2.66 kPa) to ≤ 15 mmHg (≤ 2 kPa). It is important to appreciate that these thresholds have been determined through patient outcomes in relatively small studies rather than pathophysiological evidence of ischemic damage at the cellular level.

Crucial to the interpretation of PtiO₂ in the clinical setting is the severity, duration and chronological trend of cerebral hypoxia, and not absolute PtiO₂ values in isolation, since 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 is 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 (see below).

Management of low brain tissue oxygen tension

There is currently no consensus on how low PtiO₂ 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 PtiO₂ values (figure 1). Exactly

which intervention, or combination of interventions, is most effective in improving PtiO₂ remains unclear. In fact, it appears that it is the responsiveness of the hypoxic brain to a given intervention that is the prognostic factor, with reversal of hypoxia being associated with reduced mortality [19].

Figure 1 near here

Evidence for PtiO₂-guided therapy on outcomes

There is a substantial body of evidence corroborating the relationship between low PtiO₂ values and adverse outcomes after TBI and SAH, but relatively 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 PtiO₂ values after ABI, robust evidence that this translates into improved outcomes is lacking. In TBI, most outcome-based studies of PtiO₂-guided therapy have compared standard ICP/ CPP-guided therapy with PtiO₂-guided therapy in association with ICP/ CPP-guided therapy, with conflicting findings (table 4). 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 PtiO₂, as well as variable study endpoints. Despite difficulties in controlling for these variations, a systematic review of four studies incorporating 491 patients found overall outcome benefits from PtiO₂-directed therapy compared to ICP/ CPP-guided therapy alone (odds ratio of favorable outcome = 2.1, 95% confidence interval = 1.4 - 3.1) [10]. However, all studies included in this systematic review were nonrandomized, and only two (with small sample sizes) were truly prospective.

Table 4 near here

Preliminary results have recently been released from the prospective, phase II randomized controlled brain tissue oxygen in TBI 2 (BOOST-2) trial, which evaluated the safety and efficacy of PtiO₂-directed therapy in 110 adult patients with non-penetrating severe TBI [20]. Participants were randomized to receive either treatment based on ICP monitoring and management alone (target ICP <20 mmHg) or treatment based on ICP (same target ICP) and PtiO₂ monitoring based on a pre-specified protocol to maintain PtiO₂ > 20 mmHg. The time spent with PtiO₂ < 20 mmHg was significantly lower in those in the ICP/PtiO₂ group, and there was no difference in adverse events between the two treatment arms. There was a trend towards lower overall mortality and less poor outcome in the ICP/PtiO₂ group, although these differences were not statistically significant (p = 0.229 and p = 0.221, respectively) which is unsurprising since 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 (NIR) spectroscopy (NIRS)-derived cerebral oximetry is currently the only non-invasive, 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 three decades, widespread translation into routine clinical practice has not occurred.

Technical aspects

Full technical details of the principles NIRS are beyond the scope of this review, and for further information the reader is referred elsewhere [21]. In brief, NIRS systems are based on the transmission and absorption of 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 (O₂Hb) and deoxyhemoglobin (HHb) are the most commonly measured chromophores, although cytochrome *c* oxidase (CCO), the terminal complex of the electron transfer chain, is increasingly being investigated as a marker of cellular metabolism and may prove clinically more relevant [22]. 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 three compartments. rScO₂ values are also influenced by several physiological variables including arterial oxygen saturation, PaCO₂, systemic blood pressure, hematocrit, cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral metabolic rate (CMRO₂) and cerebral arterial:venous (a:v) ratio [21].

Most commercial devices use spatially resolved spectroscopy to derive a scaled absolute hemoglobin concentration representing the relative proportions of oxy- 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 (TRS) allow measurement of absolute chromophore concentration with obvious advantages [23]. More recently, diffuse correlation spectroscopy techniques have been developed to monitor CBF and derive CMRO₂ [24, 25].

There are several concerns over the clinical application of NIRS, particularly ‘contamination’ of the signal by extracranial tissue. Some commercial cerebral oximeters use two 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 [26], and this will be 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 [27].

Indications

There are many FDA-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 very limited 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 [28].

Recent years have seen a significant increase in the use of perioperative cerebral oximetry (table 2), particularly during cardiac and carotid surgery, and surgery in the head-up (beach chair) position [21]. Although secondary ischemic injury following ABI is common, and low $rScO_2$ 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 non-invasive monitor of cerebral autoregulation, using standard signal processing techniques [29] and also novel analytical techniques of multimodal monitoring of slow wave oscillations [30]. NIRS has also been used to determine optimal CPP non-invasively in patients with TBI [31]. 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 following ABI by providing additional information about cellular metabolic failure [22].

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 upon which NIRS algorithms are based [21]. This has been used to advantage in the identification of intracranial hematomas and cerebral edema [32, 33].

Normal $rScO_2$ values and thresholds for treatment

The ‘normal’ range of rScO₂ is usually reported to lie between 60% and 75%, but there is substantial intra- and inter-individual variability; NIRS-based cerebral oximetry is therefore best considered as a trend monitor. There are no validated rScO₂-derived ischemic thresholds [21] but clinical studies and management protocols often use absolute rScO₂ values of $\leq 50\%$, or a $\geq 20\%$ reduction from baseline, as triggers for initiating measures to improve cerebral oxygenation.

Evidence of NIRS-guided therapy on outcomes

The only evidence for outcome effects of NIRS-guided treatment is from three randomized controlled trials in patients undergoing cardiac surgery [34-36] (table 5). 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 [37]. 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. Interestingly, NIRS-guided therapy may improve overall organ outcome after cardiac surgery, suggesting a role for NIRS as a monitor of overall organ perfusion [34]. 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 leads to a clinical improvement in short-term neurologic outcome in this patient population [38].

Table 5 near here

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 to other commonly used monitoring modalities, and advantages in terms of simplicity [39]. Various thresholds have been used to determine the need for shunt placement, ranging from a 10% to 20% reduction in ipsilateral rScO₂ from baseline [40]. Cerebral oximetry has higher temporal and spatial resolution compared to other modalities, and may thus find a role in guiding the manipulation of systemic physiology to minimize the risk of cerebral hypoxia/ischemia during carotid surgery [21]. 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 [41]. Distinct patterns of changes in Hb and O₂Hb were observed in ipsilateral brain cortex, suggesting that non-invasive 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 $\geq 20\%$ from baseline) was 18% [42]. 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 and other authors 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 [23].

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 [40].

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 AG, Munchberg, 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 fiber optic pulse oximetry [43], and a prototype invasive probe that combines NIRS and indocyanine green dye dilution has been investigated for the simultaneous monitoring of ICP, CBF, and CBV, avoiding NIRS signal contamination by extracerebral tissues [44].

Combined NIRS/EEG provides a unique opportunity to acquire, non-invasively and simultaneously, regional cerebral electrophysiological and hemodynamic data to elucidate on neurovascular coupling mechanisms [45]. A prototype device combining diffuse correlation spectroscopy and NIRS for the bedside measurement of CBF and cerebral oxygenation respectively has been described [46]. In the future, a single NIRS-based device may be able to provide non-invasive 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.

Conclusions

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 multi-modality neuromonitoring approach (see also chapter 7) 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

1. Duckworth JL, Stevens RD (2010) Imaging brain trauma. *Curr Opin Crit Care* 16:92–97.
2. Schell RM, Cole DJ (2000) Cerebral monitoring: jugular venous oximetry. *Anesth Analg* 90:559–566.
3. Macmillan CS, Andrews PJ (2000) Cerebrovenous oxygen saturation monitoring: practical considerations and clinical relevance. *Intensive Care Med* 26:1028–1036.
4. Rose JC, Neill TA, Hemphill JC (2006) Continuous monitoring of the microcirculation in neurocritical care: an update on brain tissue oxygenation. *Curr Opin Crit Care* 12:97–102.
5. Bouzat P, Sala N, Payen J-F, Oddo M (2013) Beyond intracranial pressure: optimization of cerebral blood flow, oxygen, and substrate delivery after traumatic brain injury. *Ann Intensive Care* 3:23.
6. Oddo M, Levine JM, Mackenzie L, et al. (2011) Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery* 69:1037–1045.
7. Kirkman MA, Smith M (2014) Intracranial pressure monitoring, cerebral perfusion pressure estimation, and ICP/ CPP-guided therapy: a standard of care or optional extra after brain injury? *Br J Anaesth* 112:35–46.
8. Muench E, Horn P, Bauhuf C, et al. (2007) Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. *Crit Care Med* 35:1844–1851.
9. van den Brink WA, van Santbrink H, Steyerberg EW, et al. (2000) Brain oxygen tension in severe head injury. *Neurosurgery* 46:868–876.
10. Nangunoori R, Maloney-Wilensky E, Stiefel M, et al. (2012) Brain Tissue Oxygen-Based Therapy and Outcome After Severe Traumatic Brain Injury: A Systematic Literature Review. *Neurocrit Care* 17:131–138.
11. Oddo M, Bösel J, and the Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring (2014) Monitoring of Brain and Systemic Oxygenation in Neurocritical Care Patients. *Neurocrit Care* 21:103–120.
12. Brain Trauma Foundation, (2007) Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 24 Suppl 1:S1–106.
13. Jaeger M, Schuhmann MU, Soehle M, et al. (2007) Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke*

- 38:981–986.
14. Kirkman MA, Smith M (2013) Supratentorial intracerebral hemorrhage: a review of the underlying pathophysiology and its relevance for multimodality neuromonitoring in neurointensive care. *J Neurosurg Anesthesiol* 25:228–239.
 15. Diringner MN, Bleck TP, Claude Hemphill J, et al. (2011) Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care* 15: 211–240.
 16. Rosenthal G, Hemphill JC, Sorani M, et al. (2008) Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. *Crit Care Med* 36:1917–1924.
 17. Johnston AJ, Steiner LA, Coles JP, et al. (2005) Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. *Crit Care Med* 33:189–195.
 18. Damiani E, Adrario E, Girardis M, et al. (2014) Arterial hypoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Critical Care* 18:711.
 19. Bohman L-E, Pisapia JM, Sanborn MR, et al. (2013) Response of Brain Oxygen to Therapy Correlates with Long-Term Outcome After Subarachnoid Hemorrhage. *Neurocrit Care* 19:320–328.
 20. Shutter L **BOOST 2 Trial Study Results**. Annual Neurocritical Care Society Meeting. (Online - available at: <http://www.neurocriticalcare.org/news/2014-annual-meeting-highlights> [last accessed on October 13, 2015]).
 21. Ghosh A, Elwell C, Smith M (2012) Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesth Analg* 115:1373–1383.
 22. Smith M, Elwell C (2009) Near-infrared spectroscopy: shedding light on the injured brain. *Anesth Analg* 108:1055–1057.
 23. Smith M (2011) Shedding light on the adult brain: a review of the clinical applications of near-infrared spectroscopy. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 369:4452–4469.
 24. Diop M, Verdecchia K, Lee TY, St Lawrence K (2011) Calibration of diffuse correlation spectroscopy with a time-resolved near-infrared technique to yield absolute cerebral blood flow measurements. *Biomed Opt Express* 2:2068–2081.
 25. Verdecchia K, Diop M, Lee T-Y, St Lawrence K (2013) Quantifying the cerebral metabolic rate of oxygen by combining diffuse correlation spectroscopy and time-resolved near-infrared spectroscopy. *J Biomed Opt* 18:27007–027007.

26. Davie SN, Grocott HP (2012) Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology* 116:834–840.
27. Kolyva C, Ghosh A, Tachtsidis I, et al. (2014) Cytochrome c oxidase response to changes in cerebral oxygen delivery in the adult brain shows higher brain-specificity than haemoglobin. *Neuroimage* 85 Pt 1:234–244.
28. Douds M, Straub E, Kent A, et al. (2014) A systematic review of cerebral oxygenation-monitoring devices in cardiac surgery. *Perfusion*.
29. Zweifel C, Castellani G, Czosnyka M, et al. (2010) Noninvasive monitoring of cerebrovascular reactivity with near infrared spectroscopy in head-injured patients. *J Neurotrauma* 27:1951–1958.
30. Highton D, Ghosh A, Tachtsidis I, et al. (2015) Monitoring cerebral autoregulation after brain injury: multimodal assessment of cerebral slow-wave oscillations using near-infrared spectroscopy. *Anesth Analg* 121:198–205.
31. Dias C, Silva MJ, Pereira E, et al. (2015) Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. *Neurocrit Care* 23:92–102.
32. Gopinath SP, Robertson CS, Contant CF, et al. (1995) Early detection of delayed traumatic intracranial hematomas using near-infrared spectroscopy. *Journal of Neurosurgery* 83:438–444.
33. Damian MS, Schlosser R (2007) Bilateral near infrared spectroscopy in space-occupying middle cerebral artery stroke. *Neurocrit Care* 6:165–173.
34. Murkin JM, Adams SJ, Novick RJ, et al. (2007) Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth Analg* 104:51–58.
35. Slater JP, Guarino T, Stack J, et al. (2009) Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann Thorac Surg* 87:36–44– discussion 44–5.
36. Deschamps A, Lambert J, Couture P, et al. (2013) Reversal of decreases in cerebral saturation in high-risk cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 27:1260–1266.
37. Zheng F, Sheinberg R, Yee M-S, et al. (2013) Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. *Anesth Analg* 116:663–676.
38. Hirsch JC, Charpie JR, Ohye RG, Gurney JG (2009) Near-infrared spectroscopy: what we know and what we need to know--a systematic review of the congenital heart disease literature. *J Thorac Cardiovasc Surg* 137:154–9–159e1–12.
39. Moritz S, Kasprzak P, Arlt M, et al. (2007) Accuracy of cerebral monitoring in

- detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. *Anesthesiology* 107:563–569.
40. Nielsen HB (2014) Systematic review of near-infrared spectroscopy determined cerebral oxygenation during non-cardiac surgery. *Front Physiol* 5:93.
 41. Kacprzak M, Liebert A, Staszkiwicz W, et al. (2012) Application of a time-resolved optical brain imager for monitoring cerebral oxygenation during carotid surgery. *J Biomed Opt* 17:016002–01600210.
 42. Salazar D, Sears BW, Andre J, et al. (2013) Cerebral desaturation during shoulder arthroscopy: a prospective observational study. *Clin Orthop Relat Res* 471:4027–4034.
 43. Phillips JP, Langford RM, Chang SH, et al. (2010) Cerebral arterial oxygen saturation measurements using a fiber-optic pulse oximeter. *Neurocrit Care* 13:278–285.
 44. Keller E, Froehlich J, Muroi C, et al. (2011) Neuromonitoring in intensive care: a new brain tissue probe for combined monitoring of intracranial pressure (ICP) cerebral blood flow (CBF) and oxygenation. *Acta Neurochir Suppl* 110:217–220.
 45. Cooper RJ, Hebden JC, O'Reilly H, et al. (2011) Transient haemodynamic events in neurologically compromised infants: a simultaneous EEG and diffuse optical imaging study. *Neuroimage* 55:1610–1616.
 46. Kim MN, Durduran T, Frangos S, et al. (2010) Noninvasive measurement of cerebral blood flow and blood oxygenation using near-infrared and diffuse correlation spectroscopies in critically brain-injured adults. *Neurocrit Care* 12:173–180.
 47. Eriksson EA, Barletta JF, Figueroa BE, et al. (2012) The first 72 hours of brain tissue oxygenation predicts patient survival with traumatic brain injury. *J Trauma Acute Care Surg* 72:1345–1349.
 48. Meixensberger J, Renner C, Simanowski R, et al. (2004) Influence of cerebral oxygenation following severe head injury on neuropsychological testing. *Neurol Res* 26:414–417.
 49. Radolovich DK, Czosnyka M, Timofeev I, et al. (2010) Transient changes in brain tissue oxygen in response to modifications of cerebral perfusion pressure: an observational study. *Anesth Analg* 110:165–173.
 50. Bohman L-E, Heuer GG, Macyszyn L, et al. (2011) Medical Management of Compromised Brain Oxygen in Patients with Severe Traumatic Brain Injury. *Neurocrit Care* 14:361–369.
 51. Ramakrishna R, Stiefel M, Udoetuk J, et al. (2008) Brain oxygen tension and outcome in patients with aneurysmal subarachnoid hemorrhage. *Journal of*

- Neurosurgery 109:1075–1082.
52. Jaeger M, Soehle M, Schuhmann MU, Meixensberger J (2012) Clinical significance of impaired cerebrovascular autoregulation after severe aneurysmal subarachnoid hemorrhage. *Stroke* 43:2097–2101.
 53. Ko S-B, Choi HA, Parikh G, et al. (2011) Multimodality monitoring for cerebral perfusion pressure optimization in comatose patients with intracerebral hemorrhage. *Stroke* 42:3087–3092.
 54. Dohmen C, Bosche B, Graf R, et al. (2007) Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. *Stroke* 38:56–61.
 55. Carvi y Nieves M, Toktamis S, Höllerhage H-G, Haas E (2005) Hyperacute measurement of brain-tissue oxygen, carbon dioxide, pH, and intracranial pressure before, during, and after cerebral angiography in patients with aneurysmal subarachnoid hemorrhage in poor condition. *Surg Neurol* 64:362–367.
 56. Jödicke A, Hübner F, Böker D-K (2003) Monitoring of brain tissue oxygenation during aneurysm surgery: prediction of procedure-related ischemic events. *Journal of Neurosurgery* 98:515–523.
 57. Ibanez J, Vilalta A, Mena MP, et al. (2003) Intraoperative detection of ischemic brain hypoxia using oxygen tissue pressure microprobes (in Spanish). *Neurocirugia (Astur)* 14:483–489.
 58. Dunham CM, Ransom KJ, Flowers LL, et al. (2004) Cerebral hypoxia in severely brain-injured patients is associated with admission Glasgow Coma Scale score, computed tomographic severity, cerebral perfusion pressure, and survival. *J Trauma* 56:482–9– discussion 489–91.
 59. Yokose N, Sakatani K, Murata Y, et al. (2010) Bedside monitoring of cerebral blood oxygenation and hemodynamics after aneurysmal subarachnoid hemorrhage by quantitative time-resolved near-infrared spectroscopy. *World Neurosurg* 73:508–513.
 60. Hametner C, Stanarcevic P, Stampfl S, et al. (2015) Noninvasive cerebral oximetry during endovascular therapy for acute ischemic stroke: an observational study. *J Cereb Blood Flow Metab*.
 61. Laflam A, Joshi B, Brady K, et al. (2015) Shoulder surgery in the beach chair position is associated with diminished cerebral autoregulation but no differences in postoperative cognition or brain injury biomarker levels compared with supine positioning: the anesthesia patient safety foundation beach chair study. *Anesth Analg* 120:176–185.
 62. Adamides AA, Cooper DJ, Rosenfeldt FL, et al. (2009) Focal cerebral oxygenation and neurological outcome with or without brain tissue oxygen-guided therapy in patients with traumatic brain injury. *Acta Neurochir (Wien)* 151:1399–1409.

63. Meixensberger J, Jaeger M, Vath A, et al. (2003) Brain tissue oxygen guided treatment supplementing ICP/ CPP therapy after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 74:760–764.
64. Stiefel MF, Spiotta A, Gracias VH, et al. (2005) Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *Journal of Neurosurgery* 103:805–811.
65. Martini RP, Deem S, Yanez ND, et al. (2009) Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. *J Neurosurg* 111:644–649.
66. McCarthy MC, Moncrief H, Sands JM, et al. (2009) Neurologic outcomes with cerebral oxygen monitoring in traumatic brain injury. *Surgery* 146:585–590.
67. Narotam PK, Morrison JF, Nathoo N (2009) Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. *J Neurosurg* 111:672–682.
68. Spiotta AM, Stiefel MF, Gracias VH, et al. (2010) Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. *J Neurosurg* 113:571–580.
69. Green JA, Pellegrini DC, Vanderkolk WE, et al. (2013) Goal Directed Brain Tissue Oxygen Monitoring Versus Conventional Management in Traumatic Brain Injury: An Analysis of In Hospital Recovery. *Neurocrit Care* 18:20–25.

Figure 1

Schematic for the management of low PtiO₂ values

CPP, cerebral perfusion pressure; EEG, electroencephalography; ETCO₂, end-tidal carbon dioxide; FiO₂, fraction of inspired oxygen; ICP, intracranial pressure; MAP, mean arterial pressure; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; PtiO₂, brain tissue oxygen tension.

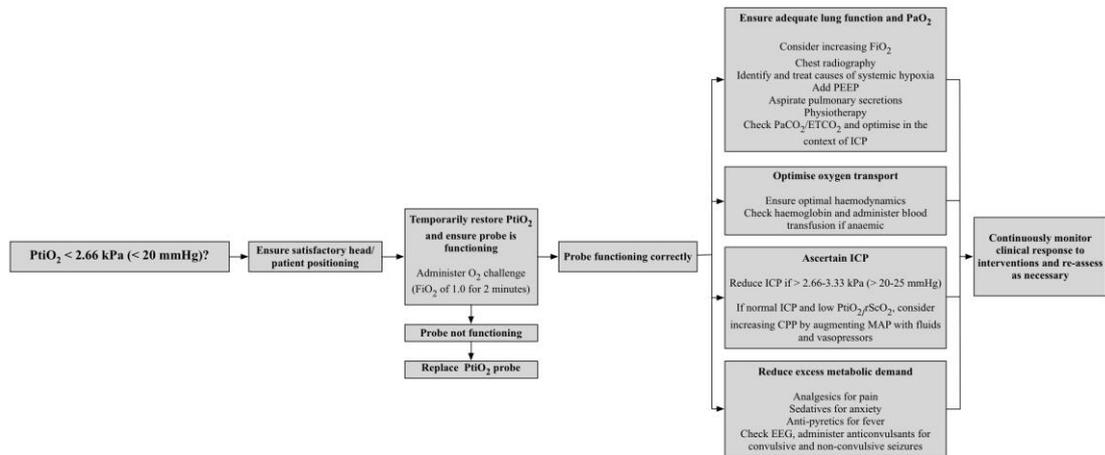


Figure 2

Axial computed tomography scan of the head demonstrating positioning of a PtiO₂ probe (arrow):

- A. in normal appearing white matter of the right frontal lobe to measure global cerebral oxygenation;**
- B. suboptimally within a contusion;**
- C. adjacent to a penumbral region to monitor cerebral oxygenation in ‘at risk’ tissue.**

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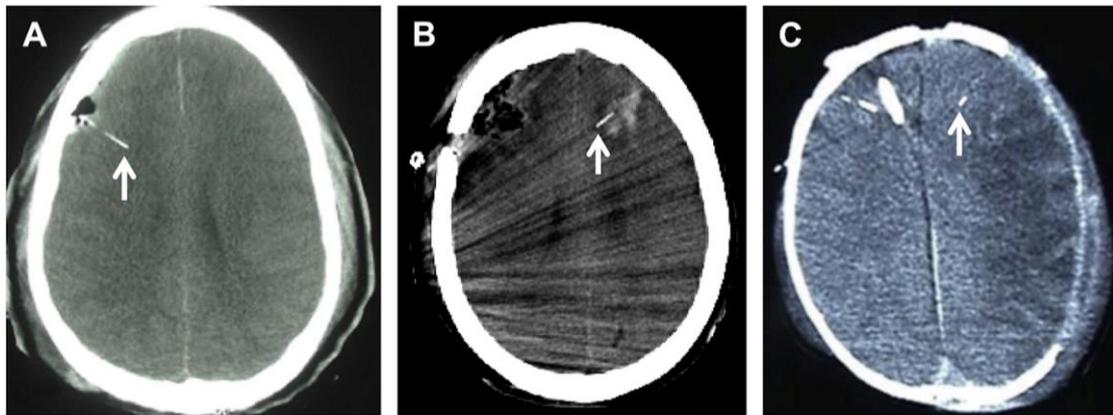


Table 1

Bedside monitors of cerebral oxygenation

	Advantages	Disadvantages
SjvO₂	<ul style="list-style-type: none"> • Real-time • Global trend monitor 	<ul style="list-style-type: none"> • Invasive insertion procedure with risk of hematoma, carotid puncture and vein thrombosis during prolonged monitoring • Insensitive to regional ischemia • Assumes stable CMRO₂ to infer CBF changes
PtiO₂	<ul style="list-style-type: none"> • Focal monitor permitting selective monitoring of critically perfused tissue • Real-time • The most effective bedside method of detecting cerebral ischemia • Relatively safe with low hematoma rate (<2%, usually small and clinically insignificant) • No reported infections 	<ul style="list-style-type: none"> • Focal monitor –the position of the probe is crucial • May miss important pathology distant from the monitored site • Invasive • Small degree of zero and sensitivity drift • One hour ‘run-in’ period required and thus critical early hypoxic/ischemic episodes may go undetected • Technical complication rates (dislocation or drift) may reach 13.6%
NIRS	<ul style="list-style-type: none"> • Real-time • High spatial and temporal resolution • Non-invasive • Assessment of several regions of interest simultaneously 	<ul style="list-style-type: none"> • Extracerebral circulation may ‘contaminate’ cerebral oxygenation measurements • Lack of standardization between commercial devices • ‘Thresholds’ for cerebral hypoxia/ischemia undetermined • Current devices only monitor relative changes in oxygenation

CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate for oxygen, CPP, cerebral perfusion pressure; ICP, intracranial pressure; NIRS, near infrared spectroscopy; PtiO₂, brain tissue oxygen tension; SjvO₂, jugular venous oxygen saturation.

Table 2

The main indications for PtiO₂ monitoring and NIRS in the perioperative and intensive care settings, based upon clinical data

Modality	Indications	Evidence	Highest quality evidence
PtiO ₂	ICU: Severe TBI	Low PtiO ₂ associated with worse mortality [47], lower GOS [6, 9], and increased neuropsychological deficits [48]	Prospective observational
		Treatment of low PtiO ₂ may improve outcomes [10, 20]	Randomized controlled trial
		PtiO ₂ can help define individual CPP thresholds [49]	Prospective observational
		Response to PtiO ₂ guided therapy associated with reduced mortality [50]	Retrospective analysis of prospective observational data
	Poor-grade SAH	Low PtiO ₂ values associated with increased mortality, but the relationship with morbidity is less clear [51]	Prospective observational
		PtiO ₂ -derived ORx autoregulation assessment can predict the risk of DCI [13] and unfavorable outcome [52]	Prospective observational
		Response to PtiO ₂ guided therapy associated with improved long-term functional outcomes [19]	Retrospective analysis of prospective observational data
	ICH	PtiO ₂ monitoring may help identify optimal CPP targets [53]	Retrospective
		Reduced peri-hematoma PtiO ₂ values associated with poor outcome [53]	Retrospective

	AIS	PtiO ₂ -derived CPP-ORx may predict the development of malignant MCA infarction [54]	Prospective observational
	Peri-operative: Cerebral angiography	Low PtiO ₂ values correlated with severe intracranial angiographic arterial caliber reduction in patients with poor-grade SAH [55]	Retrospective
	Aneurysm surgery	PtiO ₂ threshold of 15 mmHg found to be a sensitive indicator of the likelihood of developing procedure-related ischemia [56]	Prospective observational
	AVM surgery	Correlation observed between reduced PtiO ₂ values and development of a peri-probe ischemic infarction [57]	Case report
NIRS	ICU: TBI	Association between increasing length of time with rScO ₂ ≤ 60% and mortality, intracranial hypertension and compromised CPP [58]	Prospective observational
	SAH	Time-resolved NIRS was able to predict angiographic-proven vasospasm with 100% sensitivity and 85.7% specificity, and confirm vasospasm when TCD was not diagnostic [59]	Prospective observational
	AIS	May help predict cerebral edema in patients with complete MCA infarction [33]	Prospective observational
		rScO ₂ predicts poor outcome during endovascular therapy for AIS [60]	Prospective observational

Peri-operative:

Cardiac surgery	Intraoperative cerebral desaturations may be associated with more major organ morbidity and mortality [34]	Randomized controlled trial
	The role of intraoperative cerebral desaturations in postoperative cognitive decline is unclear [34, 35, 37]	Randomized controlled trial
	Intraoperative cerebral desaturations may be associated with protracted ICU [34] and hospital [35] LOS, although others disagree [36]	Randomized controlled trial
Carotid surgery	Similar accuracy and reproducibility in the detection of cerebral ischemia compared to TCD and stump pressure [39]	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 [61]	Prospective observational

AIS, acute ischemic stroke; CPP, cerebral perfusion pressure; DCI, delayed cerebral ischemia; GOS, Glasgow outcome score; ICH, intracerebral hemorrhage; ICU, Intensive Care Unit; LOS, length of stay; MCA, middle cerebral artery; NIRS, near-infrared spectroscopy; ORx, oxygen reactivity index; PtiO₂, brain tissue oxygen tension; rScO₂, regional cerebral oxygen saturation; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TCD, transcranial Doppler.

Table 3

The main variables known to influence PtiO₂ values

Systemic variables:

- Partial pressure of oxygen (PaO₂)
- Partial pressure of carbon dioxide (PaCO₂)
- Fraction of inspired oxygen (FiO₂)
- Mean arterial blood pressure
- Cardiopulmonary function
- Hemoglobin level

Brain-specific variables:

- Cerebral perfusion pressure and intracranial pressure
- Cerebral blood flow
- 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

Table 4

Summary of studies comparing outcome following brain tissue oxygen tension-directed therapy vs. intracranial pressure/cerebral perfusion pressure-directed therapy in patients with severe traumatic brain injury

Reference	Study type	PtiO ₂ -guided therapy, n	ICP/ CPP-guided therapy, n	PtiO ₂ threshold for intervention	Endpoint(s)	Principle findings
Adamides et al, 1998 [62]	Prospective	20	10	2.66 kPa (20 mmHg)	GOS at six months	No significant difference in mean GOS score between the two groups (PtiO ₂ group = 3.55, ICP/ CPP group = 4.40; p = 0.19).
Meixensberger et al, 2003 [63]	Retrospective (historical controls)	53	40	1.33 kPa (10 mmHg)	GOS at six months	A non-significant trend towards improved outcomes in the PtiO ₂ group (GOS 4 or 5 in PtiO ₂ group = 65%, in ICP/ CPP group = 54%; p = 0.27).
Stiefel et al, 2005 [64]	Retrospective (historical controls)	28	25	3.33 kPa (25 mmHg)	In-hospital mortality	Mortality rate in PtiO ₂ group (25%) significantly lower than ICP/ CPP group (44%; p < 0.05).
Martini et al, 2009 [65]	Retrospective cohort study	123	506	2.66 kPa (20 mmHg)	In-hospital mortality, FIM at hospital discharge.	Slightly worse adjusted mortality in PtiO ₂ group compared to ICP/ CPP group (adjusted mortality difference 4.4%, 95% CI = -3.9 – 13%). Worse functional outcomes at discharge in the PtiO ₂ group (adjusted FIM score difference -0.75, 95% CI = -1.41 – -0.09).
McCarthy et al, 2009 [66]	Prospective	81	64	2.66 kPa (20 mmHg)	In-hospital mortality, GOS every three	No significant difference in mortality rates between PtiO ₂ group (31%) and ICP/ CPP group (36%; p =

					months post-discharge.	0.52). A non-significant trend towards improved outcome (GOS 4 or 5) in PtiO ₂ group (79%) compared to ICP/ CPP group (61%; p = 0.09).
Narotam et al, 2009 [67]	Retrospective (historical controls)	139	41	2.66 kPa (20 mmHg)	GOS at six months	Higher mean GOS score in PtiO ₂ group (3.55 ± 1.75) compared to ICP/ CPP group (2.71 ± 1.65; p < 0.01). OR for good outcome in PtiO ₂ group = 2.09 (95% CI = 1.03 - 4.24). Reduced mortality rate in the PtiO ₂ group (26% versus 41.5%; RR reduction 37%) despite higher ISS scores in PtiO ₂ group.
Spiotta et al, 2010 [68]	Retrospective (historical controls)	70	53	2.66 kPa (20 mmHg)	In-hospital mortality, GCS at three months	Mortality rates significantly lower in PtiO ₂ group (26%) than ICP/ CPP group (45%; p < 0.05). A favorable outcome (GOS score of 4 or 5) was also observed more commonly in the PtiO ₂ group (64% vs. 40%; p = 0.01).
Green et al, 2013 [69]	Retrospective cohort study	37	37	2.66 kPa (20 mmHg)	In-hospital mortality, GOS and FIM at discharge	No survival difference offered by PtiO ₂ -guided therapy (64.9% vs. 54.1%, p = 0.34), or difference in discharge GCS or FIM. Of note, the PtiO ₂ -guided therapy group had significantly lower ISS at baseline.
Shutter et al. 2014 [20]	Prospective phase II RCT	53	57	2.66 kPa (20 mmHg)	Proportion of time PtiO ₂ <20 mmHg, safety, feasibility of protocol implementation, non-futility (mortality, GOS-extended at 6	Median proportion of time with PtiO ₂ <20mmHg significantly lower in the ICP/ PtiO ₂ group (0.14) compared to the ICP group (0.44, p<0.00001). No significant difference between adverse events, and protocol violations were infrequent. Lower overall mortality and poor outcome on the 6-month GOS-

months)

extended in the ICP/ PtiO₂ group, but neither reached statistical significance (p=0.229 and p=0.221, respectively).

CI, confidence interval; CPP, cerebral perfusion pressure; FIM, functional independence measure; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score; ICP, intracranial pressure; ISS, injury severity score; LOS, length of stay; MAP, mean arterial pressure; OR, odds ratio; PtiO₂, brain tissue oxygen tension; RCT, randomized controlled trial; RR, relative risk.

Table 5

Summary of the randomized studies evaluating outcomes following near-infrared spectroscopy-guided management of cerebral desaturations

Reference	Surgery type	Intervention arm, n	Control arm, n	Target rScO ₂ values in intervention arm	Endpoint(s)	Principle findings
Murkin et al. 2007 [34]	CABG	100	100	≥75% of baseline threshold	30 day postoperative morbidity and mortality	Prolonged cerebral desaturations (p = 0.014) and ICU stay observed in the control group (p = 0.029). MOMM* higher in the control group (p = 0.048) and associated with lower baseline and mean rScO ₂ , more cerebral desaturations, longer ICU and hospital LOS.
Slater et al. 2009 [35]	CABG	125	115	≥80% of baseline threshold	Cognitive function (using a battery of tests) up to 3 months and hospital LOS	A high rScO ₂ desaturation score (>3000%-second) associated with early postoperative cognitive decline (p = 0.024) and hospital stay >6 days (p = 0.007). Benefits of the intervention on cognitive outcomes lost in multivariate analysis.
Deschamps et al. 2013 [36]	High-risk cardiac surgery**	23	25	≥80% of baseline threshold for 15 seconds	Desaturation load (% desaturation x time), ICU and hospital LOS	Half of the patients had cerebral desaturations that could be reversed 88% of the time. Interventions resulted in smaller desaturation loads in the operating room and ICU. No difference in hospital or ICU LOS.

* 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 >48 h.

** Desaturation score calculated by multiplying rScO₂ less than 50% by duration in seconds,

*** 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.*

CABG, coronary artery bypass grafting; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; rScO₂, regional cerebral oxygen saturation.