Shedding light on the adult brain: a review of the clinical applications of near-infrared spectroscopy

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Near-infrared spectroscopy (NIRS) has potential as a non-invasive brain monitor in a wide range of clinical scenarios. In the last decade, there has been a rapid expansion of clinical experience using NIRS to monitor cerebral oxygenation, particularly in cardiac surgery, where there is some evidence that NIRS-guided brain protection protocols might lead to a reduction in peri-operative neurological complications. There are no data to support the wider application of NIRS to monitor cerebral oxygenation during routine anaesthesia and surgery, and its application in brain injury, where it might be expected to have a key monitoring role, is as yet undefined. Technological developments, including the introduction of broadband and time-resolved spectrometers that are capable of reliably measuring changes in oxidized cytochrome c oxidase, offer real potential for a single NIRS-based device to provide multi-site, regional monitoring of cerebral metabolic status as well as oxygenation and haemodynamics.

Keywords: near-infrared spectroscopy; brain injury; cerebral oxygenation; cerebral metabolism

1. Introduction

In this journal in 1997, Kirkpatrick established a case for the use of near-infrared spectroscopy (NIRS) for monitoring the adult brain [1]. In this review, I will develop that theme and examine progress in the intervening decade. Specifically, I will examine the evidence for the clinical application of NIRS monitoring of the healthy but ‘at risk’ brain, as well as its potential roles in monitoring the injured brain. I will call on the experience of our research group to illustrate the application of novel NIRS techniques to quantify cerebral oxygenation, haemodynamic and metabolic changes, and to discuss the potential value of integrating NIRS-derived variables into routine bedside multi-modal cerebral monitoring to guide brain-directed therapies.

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2. Pathophysiology of brain injury and the role of monitoring

It is not within the remit of this paper to discuss the pathophysiology of acute brain injury in detail, but it is important to highlight some key aspects to put the role of brain monitoring into context. Brain injury, particularly traumatic brain injury, is traditionally classified into primary and secondary injury, although this delineation is somewhat artificial. Primary injury occurs as a result of mechanical forces applied to the brain at the time of injury or because of primary haemorrhagic and ischaemic events. This leads to secondary injurious processes, including ionic, metabolic and inflammatory changes, which worsen the primary injury and adversely affect outcome. Intracranial and systemic physiological insults, particularly hypotension, hypoxaemia and raised intracranial pressure, are also potent causes of on-going (‘secondary’) brain injury. Although the pathophysiology of brain injury is complex, two components are of key importance—reduction in substrate delivery below critical thresholds and impaired mitochondrial substrate utilization leading to cerebral cellular energy failure. Although some pathophysiological processes are disease specific, the final common path is cerebral hypoxia/ischaemia across a wide spectrum of disorders.

It is important to note that hypoxia/ischaemia does not result specifically from a reduction in cerebral blood flow, but rather from a mismatch between blood flow and cerebral metabolic demand. Although time-critical windows to prevent or minimize permanent ischaemic neurological injury exist, these are likely to be disease specific and, in any case, often pass silently because the bedside detection of cerebral hypoxia/ischaemia in real time remains problematic [2]. Measurement of cerebral oxygenation is widely used to assess the balance between cerebral metabolic supply and demand, but standard methods have significant limitations. Some, such as jugular venous oximetry, are global and may miss regional ischaemia, whereas others, such as brain tissue oxygen tension, are focal and identification of ischaemia is crucially dependent on the position of the probe. Furthermore, these techniques are invasive and not usually available outside specialist centres. Non-invasive techniques, such as trans-cranial Doppler ultrasonography or electroencephalography (EEG), are used to assess indirectly the adequacy of cerebral blood flow or the presence of ischaemia, respectively, but trans-cranial Doppler is significantly operator dependent and the EEG is difficult to interpret by non-specialists [3].

There is therefore a need for a non-invasive, bedside monitor that can provide reliable and real-time data from several regions of the brain simultaneously. NIRS is a non-invasive technique that offers the potential for bedside monitoring of cerebral oxygenation, haemodynamics and metabolic status over multiple regions of interest. However, despite the potential of NIRS to address many of the shortcomings inherent in other cerebral monitoring techniques, there has been limited adoption into clinical practice more than three decades since its first description.

3. Commercially available near-infrared spectroscopy systems

There are several commercial NIRS systems, and non-commercial prototypes, available for brain monitoring [4]. Most commercial devices are oximeters
incorporating spatially resolved spectroscopy, although time-resolved and frequency-domain (also known as phase modulation) spectroscopy systems are now being introduced to the market. The technical aspects of commercially available NIRS devices have recently been reviewed in detail elsewhere [4].

The availability of many clinical systems has, until recently, been limited to Europe and Japan because few instruments have historically been approved by the US Food and Drug Administration. However, this situation is changing, and commercially available NIRS systems currently include the INVOS series (Somanetics Corporation, Troy, MI, USA), FORE-SIGHT (CAS Medical Systems, Branford, CT, USA), Nonin 7600 (Nonin Medical, Plymouth, MN, USA), Oxiplex TS (ISS, IL, USA) and the NIRO series (Hamamatsu Photonics KK, Hamamatsu City, Japan).

Unfortunately, there is a lack of standardization between commercially available NIRS devices. Different manufacturers use different nomenclature, although most do provide an absolute measure of regional cerebral tissue saturation (rScO₂) in some form and display this as a simple percentage value. However, the algorithms used, and even the variables actually measured, vary between systems, and this leads to difficulty when selecting devices for clinical use and when comparing between devices or clinical studies using different devices [5,6]. Of particular relevance is the observation that the application of different algorithms produces significantly different chromophore concentrations from the same underlying optical data [7]. Several studies have demonstrated substantial differences in rScO₂ measured by cerebral oximeters from different manufacturers, highlighting the crucial importance of being able to understand the algorithm on which a particular device relies [8,9]. Unfortunately, some manufacturers do not publish their algorithms, rendering data from such devices of uncertain validity and making it impossible to compare data between devices.

Because NIRS interrogates arterial, venous and capillary blood within the field of view, the derived saturation represents a ‘tissue’ oxygen saturation measured from these three compartments that can be used to identify cerebral hypoxia/ischaemia [10]. This is the rationale for the application of cerebral oximetry in the clinical setting. Current commercially available NIRS devices are usually designed to be placed on the forehead and, as with other regional monitoring techniques, it is impossible to detect changes in areas located distant from the monitored site, although global cerebral oxygen sufficiency can be evaluated [11]. Multi-probe NIRS devices are now available and these provide regional measurements from multiple areas simultaneously. This is particularly important given the significant regional heterogeneity in the injured brain.

### 4. Current clinical applications of near-infrared spectroscopy

Despite interest in the clinical application of NIRS for more than three decades, widespread translation into routine clinical practice has not yet occurred. There is some recent evidence that treatment guided by NIRS can improve clinical outcome in specific clinical scenarios, particularly those where there is an increased risk of cerebral ischaemic injury, but thus far there is no evidence to support the widespread introduction of NIRS as a monitor of cerebral well-being.
In particular, there is little evidence to support its routine application during general anaesthesia and surgery, despite enthusiastic endorsement for this indication by several manufacturers of NIRS devices.

(a) Cardiac surgery

Poor neurological outcome is a major concern after cardiac surgery, particularly in patients undergoing cardiopulmonary bypass. Stroke occurs in 1–3 per cent of patients, but this is overshadowed by the development of long-standing post-operative cognitive dysfunction in more than 50 per cent. Likely mechanisms of injury include emboli and cerebral hypoperfusion, and a variety of management protocols have been introduced to minimize these risks. However, it is the introduction of NIRS-guided ‘brain protection’ protocols aimed at optimizing cerebral oxygen delivery during cardiopulmonary bypass that has recently generated substantial interest [13,14].

Case-control and retrospective studies show a correlation between cerebral desaturation and adverse outcome after cardiopulmonary bypass, and improvements in outcome, including a reduced incidence of stroke, which are linked to cerebral oximetry monitoring during bypass [15,16]. However, such clear outcome benefits have not been identified in prospective trials. In one such study, 200 patients undergoing coronary artery bypass grafting were randomized to a control arm where rScO$_2$ was monitored using the INVOS 5100 oximeter but not displayed, and an intervention arm where a protocol to augment cerebral oxygen delivery, based on changes in rScO$_2$, was implemented [17]. The protocol was targeted to restore rScO$_2$ to baseline, and intervention led to rapid improvement in rScO$_2$ in 84 per cent of cases. Although there was no overall difference in the incidence of adverse complications between the two groups, there were fewer strokes and other major organ morbidity in the intervention group. Baseline and mean rScO$_2$ values were lower, and there were more episodes of cerebral desaturation, in patients who died or who developed major organ morbidity, suggesting that rScO$_2$ might be a useful surrogate marker for poor outcome after cardiopulmonary bypass. A study using a similar protocol in 265 patients undergoing coronary artery bypass grafting assessed the burden of cerebral ischaemia as the amount of time that rScO$_2$ was less than 50 per cent (measured by the INVOS 5100) and found that this was associated with an increased risk of cognitive decline and prolonged hospital stay [18]. Such data suggest that the duration as well as the degree of cerebral desaturation determine the overall ischaemic burden, raising the possibility that it is a time-dependent exposure to a certain threshold of cerebral ischaemia (a viability-time threshold) that leads to irreversible tissue damage and subsequent functional impairment, a concept supported by data from animal studies (see below) [19].

Despite conflicting outcome data, NIRS is being increasingly used to monitor cerebral oxygenation during cardiac surgery because of the lack of use-associated risk and modest cost [20]. It has recently been suggested that the potential benefits of NIRS monitoring during very high-risk procedures (such as hypothermic circulatory arrest) might be enhanced by novel interpretative techniques that use mathematical modelling of NIRS variables to quantify time limits for cerebral hypoxia/ischaemia [21].
Because rScO₂ is a measure of (brain) tissue oxygen saturation, it has been suggested that it might also indirectly reflect the adequacy of the systemic circulation and therefore of cardiopulmonary function. A recent observational study prospectively investigated the effect on mortality and cardiopulmonary morbidity of pre-operative rScO₂ measured with an INVOS 4100 or a 5100 cerebral oximeter in 1178 patients undergoing cardiac surgery with cardiopulmonary bypass [22]. The lowest median (range) oxygen-supplemented pre-operative rScO₂ was 64 per cent (15–92%). Low pre-operative rScO₂ was significantly correlated with post-operative biomarkers of cardiac and renal injury, and with cardiac dysfunction (p < 0.001). rScO₂ was lower in those who had died by 30 days compared with those who survived [median (95% confidence interval) 58% (50.7–62.0%) versus 64% (64–65%), respectively, p < 0.001], and pre-operative rScO₂ less than 50 per cent was an independent risk factor for 30 day and 1 year mortality. The authors suggest that their data support a link between low rScO₂ and cardiopulmonary dysfunction and, because low rScO₂ is associated with morbidity and mortality, hypothesize that it might be a useful addition to the pre-operative risk stratification of patients undergoing cardiopulmonary bypass as well as a potential non-invasive technology for guiding therapy in patients with heart failure. As is so often the case in clinical NIRS studies, there is no debate about the validity and reproducibility of the technology in the particular scenario, although the authors do acknowledge that the INVOS is only approved as a trend monitor and that they used it here to make ‘one-off’ measurements in isolation. There is no discussion of the large variability (15–92%) of the baseline value of rScO₂ or the clinical relevance of such observations. Notwithstanding these comments, this study brings an interesting angle to the debate about the clinical applications of NIRS, and further investigation in this area is warranted.

(b) Carotid endarterectomy

Carotid endarterectomy involves a period of carotid occlusion and an associated risk of critical cerebral ischaemia if collateral blood supply is insufficient. Although this risk can be minimized by use of a shunt to maintain cerebral blood flow during the period of occlusion, placement of the shunt is itself associated with substantial risks, particularly of atheromatous emboli. Several methods are used to assess the likely adequacy of collateral supply, and therefore of cerebral oxygen delivery, during the cross-clamp period to inform the decision regarding shunt placement. When carotid endarterectomy is performed under regional anaesthesia, alteration of mentation is the best monitor of impending ischaemia and an indication for shunt placement. However, general anaesthesia is required in many circumstances, so surrogate measures of cerebral ischaemia, including EEG and trans-cranial Doppler, have been used. NIRS offers advantages over these techniques in terms of simplicity and has been employed in some centres as the primary cerebral monitor during carotid endarterectomy for more than 10 years. In such circumstances, a 20 per cent reduction in rScO₂ from baseline is widely used as the ‘threshold’ for shunt placement or other interventions to increase cerebral oxygen delivery [23].

The application of NIRS during carotid endarterectomy has been compared with established monitoring techniques and is the subject of a recent review [24]. In 594 patients undergoing carotid endarterectomy with general anaesthesia, the
sensitivity, specificity and predictive values of various rScO2 thresholds indicating the need for shunt placement or causing neurological complications were assessed [25]. rScO2 was measured using either an INVOS 3100-A or a 4100-SSA cerebral oximeter, and a 12 per cent decrease from baseline was optimal, having a sensitivity of 75 per cent, a specificity of 77 per cent, and positive and negative predictive values of 37 per cent and 98 per cent, respectively. In this study, the previously applied threshold of a 20 per cent reduction in rScO2 from baseline had a low sensitivity (30%) but a very high specificity (98%), with positive and negative predictive values of 37 per cent and 98 per cent, respectively. Other studies have demonstrated similar accuracy and reproducibility for NIRS in the detection of cerebral ischaemia compared with other monitoring modalities [26].

Many investigators have attempted to define an absolute threshold for determination of impending cerebral hypoxia/ischaemia during carotid endarterectomy. In one, EEG was used to define the presence of cerebral ischaemia after carotid artery clamping, and no patient with a reduction in the tissue oxygenation index (TOI), a NIRO 300-derived measure of rScO2, of less than 13 per cent developed EEG evidence of ischaemia [27]. In another study, an independent neurologist evaluated clinical and EEG signs of cerebral ischaemia in 50 patients undergoing carotid endarterectomy with regional anaesthesia, and the average percentage reduction in rScO2 from baseline, measured using the INVOS 4100, during carotid clamping was 17 per cent in patients who developed signs of ischaemia and only 8 per cent in those who did not (p = 0.01) [28]. Although a decrease in rScO2 of 15 per cent or more during carotid clamping in this study was associated with a 20-fold increase in the odds for developing cerebral ischaemia, this threshold only had a 44 per cent sensitivity, 82 per cent specificity and a negative predictive value of 94 per cent. Another study using EEG as the comparator has identified reductions in rScO2 from baseline between 5 and 25 per cent as potential ischaemic thresholds [29]. A recent study failed to show a reliable correlation between rScO2 and stump pressure [30]. It is therefore currently impossible to specify an accurate NIRS-derived rScO2 threshold that can be widely applied to guide shunt placement, or detect cerebral hypoxia/ischaemia, during carotid endarterectomy. However, optimism remains that it might in the future be possible to use NIRS to guide systemic physiological management in order to optimize cerebral perfusion and oxygenation during carotid surgery [31].

(c) Routine brain monitoring during anaesthesia

Although the primary endpoint of general anaesthesia is its effect on the brain, this organ remains the least monitored during anaesthesia and surgery. The potential to monitor cerebral well-being continuously, particularly when the brain might be at risk because of dysautoregulation or hypoperfusion, is of course an attractive proposition, since prolonged reductions in systemic blood pressure that exceed (unknown) critical thresholds for adequate cerebral perfusion (in terms of both severity and duration) may result in permanent neurological injury. Because NIRS allows immediate recognition of cerebral desaturation events that are undetected by conventional intra-operative monitoring, it has been suggested that it should be introduced more widely into clinical practice [32]. Although enthusiasts argue that early detection of cerebral desaturation will lead to targeted intervention that will improve peri-operative outcome, the evidence for such benefit has thus far proved elusive.
In one study, rScO2 was monitored continuously using an INVOS 3100A oximeter in 16 patients undergoing orthoptic liver transplantation, and clamping the recipient’s liver led to a significant decline in rScO2 in 50 per cent of the patients [33]. This cerebral desaturation correlated significantly with post-operative increases in neuron-specific enolase and protein S-100B, biomarkers of hypoxia/ischaemia-related cerebral damage. However, there were no significant differences in haemodynamic variables between patients with and without reductions in rScO2, so potential targets for its prevention are unclear. In another study, a cohort of otherwise healthy elderly patients undergoing non-vascular abdominal surgery were randomly allocated to an intervention group (n = 56), in which rScO2 measured using an INVOS 4100 oximeter was maintained at 75 per cent or more of baseline, or to a control group (n = 66), where anaesthesia was managed routinely and rScO2 was monitored but not displayed [34]. Although the overall mean (95% confidence interval) rScO2 was higher in patients in the intervention group than in the control group (66% (64–68%) versus 61% (59–63%), respectively, p = 0.002), there was no difference in the incidence of cerebral desaturation between the two groups—rScO2 fell below 75 per cent of baseline in 11 (20%) and 15 (23%) of patients in the intervention and control groups, respectively (p = 0.82). However, control patients with intra-operative cerebral desaturation had a lower Mini Mental State Examination score on the seventh post-operative day and longer hospital length of stay than patients in the intervention group (p = 0.02). The failure of the intervention to prevent cerebral desaturation in 20 per cent of patients merits further consideration if such protocols are to be introduced more widely.

There has been most recent interest in the application of NIRS during surgery on patients operated on in the 45–90° head-up position (often called the beach chair position) because they may be at (minimal) risk for adverse neurological events. It is hypothesized that the unopposed hypotensive effects of the upright position consequent on the attenuation by anaesthesia of normal autonomic responses, in association with the direct vasodilating effects of anaesthetic agents, might lead to cerebral desaturation [35]. In one study, the incidence of cerebral desaturation, defined as a 20 per cent or more reduction in rScO2 from baseline, or as an absolute value of rScO2 55 per cent or less for more than 15 s, measured using the FORE-SIGHT device, was compared in 124 patients undergoing shoulder surgery under general anaesthesia in the beach chair or lateral decubitus positions [36]. Although intra-operative haemodynamic variables did not differ between the two groups, rScO2 values were lower in the beach chair position group throughout the intra-operative period (p < 0.0001). The incidence of cerebral desaturation was also higher in the beach chair position compared with the lateral decubitus position (80.3% versus 0%, respectively, p = 0.0001), as was the median number of cerebral desaturation events per subject (4, range 0–38, versus 0, range 0–0, respectively, p < 0.0001). While impressive at first glance, these data require further consideration. First, this apparently high incidence of cerebral desaturation does not easily relate to the exceedingly low incidence of post-operative neurological damage in the huge numbers of patients who undergo surgery in the head-up position each year. It is also not clear what these episodes of ‘cerebral desaturation’ actually represent. Cardiorespiratory variables (the ‘input’ to the brain) were unaffected by the operative position and the cerebral metabolic rate is unlikely to have changed substantially during
the study period. It is therefore important that further studies are undertaken to determine whether potentially confounding effects, such as position-related changes in tissue geometry, might contribute to the measured changes in rScO2 under such circumstances.

5. Brain injury

The logical application for a non-invasive, real-time cerebral monitor is after acute brain injury, where secondary ischaemic injury is common and associated with adverse outcome. However, this is an area where there has been limited research of the utility of NIRS, and no outcome studies. This is in part related to the significant difficulties in the application of NIRS after brain injury, not least because the challenges of describing NIRS variables in the normal brain are accentuated by the optical complexity of oedematous brain tissue and the presence of intracranial haematomas. These factors have in fact been used to advantage in studies using NIRS to identify intracranial haematomas [37] and cerebral oedema [38].

(a) Monitoring cerebral oxygenation after brain injury

To date, studies of NIRS in adult brain injury have been observational and highlight two key difficulties in investigating cerebral oxygenation in this context—the problem of defining a threshold for hypoxia/ischaemia, particularly in the presence of acutely disordered cerebral metabolic function, and the lack of a gold standard against which NIRS-derived variables can be compared [39]. It is also of note that structurally and physiologically different regions of the brain are monitored by different modalities, making comparison between monitors (including NIRS) difficult.

One study identified an association between the increasing length of time that rScO2 (measured with an INVOS 4100 oximeter) was below 60 per cent and intracranial hypertension, low cerebral perfusion pressure and increased mortality in 18 patients with severe traumatic brain injury [40]. A more recent study found that brain tissue oxygen tension and rScO2 (measured using an INVOS 5100) were directly and significantly related in 22 patients with severe traumatic brain injury [41]. rScO2 less than 60 per cent predicted ‘severe’ brain hypoxia, defined in this study as brain tissue oxygen tension less than 1.6 kPa, with a sensitivity and specificity of 73 per cent and 86 per cent, respectively, whereas the sensitivity and specificity of rScO2 less than 70 per cent for ‘moderate’ brain hypoxia (brain tissue oxygen tension 1.6–2.0 kPa) was only 62 per cent and 49 per cent. The authors concluded that (non-invasive) rScO2 monitoring cannot be considered a substitute for routine (invasive) brain tissue oxygen tension monitoring.

There has also been interest in the application of rScO2 monitoring to detect cortical changes related to cerebral vasospasm after aneurysmal subarachnoid haemorrhage. In a case series of 32 patients undergoing endovascular treatment of a ruptured cerebral aneurysm, there was a correlation between the rate of decline of ipsilateral rScO2 measured using an INVOS 3100 oximeter and vasospasm confirmed by digital subtraction angiography, with the rate of decline in rScO2 being 3.5% min\(^{-1}\) greater in patients with vasospasm than in those without [42]. A recent study used time-resolved spectroscopy (TRS-20, Hamamatsu Photonics)
to make repeated measurements of cortical oxygen saturation (CoSO$_2$) and haemoglobin concentration in 14 patients over a 14 day period after subarachnoid haemorrhage [43]. In six patients with only small temporal changes in CoSO$_2$ (less than 5% from baseline) and stable haemoglobin concentrations, there was no angiographic evidence of cerebral vasospasm. In contrast, there was an abrupt fall in CoSO$_2$ and total haemoglobin concentration between days 5 and 9 after subarachnoid haemorrhage in eight patients, six of whom had severe vasospasm confirmed by angiography. The onset of vasospasm was associated with a significant decrease in CoSO$_2$ ($p = 0.007$) and in total ($p = 0.0038$) and oxyhaemoglobin ($p = 0.0025$) concentrations—changes that are suggestive of cortical ischaemia. Interestingly, trans-cranial Doppler failed to detect vasospasm in four of the six cases that were correctly diagnosed by time-resolved spectroscopy, presumably because NIRS detects changes in the cerebral cortex and trans-cranial Doppler those in basal vessels. This is of potential clinical relevance because many of the neurological deficits that result from vasospasm are related to cortical ischaemia. From their data, the authors estimated a 3.9–6.4 per cent reduction in CoSO$_2$ from baseline as the cut-off values predicting vasospasm with high sensitivity (100%) and specificity (85.7%). Also of interest is the finding of significantly higher CoSO$_2$ ($p = 0.048$) and lower deoxyhaemoglobin concentration ($p = 0.002$) in patients on day 1 after subarachnoid haemorrhage compared with controls. The authors speculate that, because there was no associated change in the total haemoglobin concentration, this implies a reduction in cerebral oxidative metabolism, rather than hypoperfusion. There is some evidence that aneurysmal subarachnoid haemorrhage is associated with a reduction in oxidative metabolism [44], and the potential for NIRS to monitor this is an exciting possibility. Another novel aspect of this study was the use of image-guided positioning of the NIRS optodes to facilitate consistent monitoring of the same cortical area on consecutive days. This approach addresses one of the factors limiting the repeatability of NIRS measurements over time.

(b) Viability-time thresholds of cerebral hypoxia/ischaemia

Although low rScO$_2$ has been associated with poor outcome after brain injury [40], the application of NIRS in outcome studies, or to guide treatment, is hampered by the absence of a gold standard for comparison, as well as by the inability to define NIRS-derived ‘thresholds’ for cerebral hypoxia/ischaemia [39]. Viability-time thresholds for brain tissue hypoxia/ischaemia have been studied most widely in adult stroke research, where the concept of ‘time is brain’ is increasingly recognized, and interventions to restore perfusion prior to the onset of irreversible tissue damage are associated with improved functional outcomes [45]. While the mechanisms of injury and potential interventions are different in other types of brain injury, it is likely that similar windows for targeted intervention can be identified [46,47]. The use of NIRS to identify rScO$_2$-derived viability-time thresholds predictive of neurological outcome is therefore an attractive proposition that would have wide clinical application.

In one study, a piglet model was used to investigate the temporal development of brain damage when rScO$_2$ was maintained at 35 per cent, a threshold previously demonstrated by the same group to be associated with neurophysiological impairment [19]. Hypoxia/ischaemia lasting 2h or less was
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not associated with subsequent neurological deficit, whereas, for longer episodes of hypoxia/ischaemia, the incidence of neurological injury increased by about 15% h\(^{-1}\) and was heralded by abnormalities in NIRS variables during reperfusion. These findings suggest not only that it is possible to define a viability-time threshold using rScO\(_2\), but also that a several-hour window of opportunity exists during severe hypoxia/ischaemia that might be used to deliver targeted neuroprotective strategies and potentially prevent or minimize irreversible tissue damage and subsequent neurological injury. The possibility that NIRS might identify treatment windows before irreversible tissue changes have occurred, and that changes during reperfusion might also predict outcome, is an exciting prospect.

(c) Monitoring cerebral autoregulation after brain injury

Cerebrovascular autoregulation is frequently impaired after brain injury and is associated with poor outcome because it renders the brain more susceptible to ischaemic insults. Cerebrovascular pressure reactivity is a key component of cerebrovascular autoregulation and has been incorporated into several bedside methods of assessing autoregulation. These include the pressure reactivity index (PRx), the moving correlation between slow waves in arterial blood pressure and intracranial pressure, and the mean velocity index (Mx), where trans-cranial Doppler-measured blood flow velocity is substituted for intracranial pressure [48]. Pressure reactivity and mean velocity indices can be monitored continuously and have been used to define individual brain-directed targets and improve outcome after head injury [49].

Cerebral autoregulation has recently been assessed non-invasively using NIRS-derived haemoglobin variables in 40 patients with severe traumatic brain injury [50]. In this study, there was a significant correlation (\(r = 0.49, p < 0.001\)) between THx, a measure of autoregulation derived from the total haemoglobin index (measured using spatially resolved spectroscopy with a Hamamatsu NIRO 200) and arterial blood pressure, and the PRx. The same group has also demonstrated a correlation between TOIx, a measure of autoregulation derived from the TOI (Hamamatsu NIRO 200), and the Mx in a group of 27 patients following poor-grade subarachnoid haemorrhage [51].

Although NIRS-derived indices of cerebrovascular autoregulation are related to both pressure reactivity and mean velocity indices, agreement is limited by the complex and nonlinear relationships between intracranial pressure, flow velocity and NIRS variables. Specific frequency bands that characterize autoregulatory processes with analysis in the time and frequency domains may more accurately identify the relationship between NIRS and other signals, including those features that are most closely related to autoregulation. In particular, wavelet-based techniques aid the interpretation of complex time-variant signals, since they focus analysis to specific features of interest within the time and frequency domains simultaneously, producing qualitative and quantitative evidence of cerebrovascular autoregulation that is not possible using other methods [52]. This is an interesting area of research that is likely to translate readily into clinical practice. Figure 1 shows an example of how NIRS monitoring of cerebrovascular autoregulation can be optimized using a wavelet analysis technique.
Figure 1. Monitoring cerebral autoregulation with near-infrared spectroscopy. The upper panels show the individual mean arterial blood pressure (MAP), trans-cranial Doppler-derived blood flow velocity (TCD), intracranial pressure (ICP) and NIRS-derived (NIRO 100, Hamamatsu Photonics) total haemoglobin concentration (HbT) waveforms from a single patient. Note the almost identical cyclic activity. The lower panels demonstrate the wavelet transform of the MAP and HbT signals together with a comparison of their phase. The darker red appearance of the lower plot indicates high agreement in phase alignment across the frequencies shown (1–0.003Hz) and therefore absence of cerebral autoregulation. (Adapted from D. Highton 2011, unpublished observations. Reproduced by permission.)

(d) Monitoring metabolic failure after brain injury

The importance of cellular energy failure as a key component of the pathophysiology of acute brain injury is now well recognized, and cerebral cellular energy status has been quantified at the bedside using cerebral
Figure 2. Changes in cerebral cytochrome c oxidase concentration during hypoxaemia in healthy volunteers. (a) The changes in estimated cerebral oxygen delivery (ΔecDO₂), haemoglobin difference concentration (Δ[Hbdiff]) and CCO concentration (Δ[CCO]), measured using a custom-made broadband spectroscopy system, between hypoxia and baseline in healthy adults. (b) The correlation of ΔecDO₂ and Δ[CCO] and Δ[Hbdiff]. The box-and-whisker plots show group median and interquartile range. Significant differences between hypoxia and baseline are indicated by *p < 0.05, **p < 0.01, ***p < 0.001 and ****p < 0.0001. (Adapted from Tisdall, M. 2009 Non-invasive near-infrared spectroscopy: a tool for measuring cerebral oxygenation and metabolism in patients with traumatic brain injury. MD thesis, University College London. Reproduced by permission.)

microdialysis [53]. Cytochrome c oxidase (CCO) is the terminal electron acceptor in the mitochondrial electron transport chain and responsible for over 95 per cent of oxygen metabolism; its oxidation status reflects the balance between cerebral energy supply and demand. NIRS-derived measurement of CCO has been validated as a measure of cellular energy status in animal models [54] and offers the potential to assess cerebral mitochondrial redox state, and the adequacy of oxygen delivery and utilization, after human brain injury [39].
Our group has recently developed and tested in healthy volunteers and brain-injured patients a multi-modal monitoring strategy that incorporates a novel multi-wavelength NIRS system optimized for CCO measurement in adults. In a study in healthy adult volunteers, we used a custom-built broadband spectroscopy system to measure changes in the cerebral concentrations of oxidized CCO ($\Delta[CCO]$), oxyhaemoglobin ($\Delta[HbO_2]$) and deoxyhaemoglobin ($\Delta[HHb]$) during arterial hypoxaemia, and related these to changes in estimated cerebral oxygen delivery ($\Delta ecDO_2$) [55]. At the nadir of hypoxaemia (SpO2 approx. 80%), the median (interquartile range) $ecDO_2$ decreased by 9.2 (5.4–12.1) per cent ($p < 0.0001$), and this was associated with an increase in total haemoglobin concentration ($\Delta[HbT] = \Delta[HbO_2] + \Delta[HHb]$) of 2.83 (2.27–4.46) μmol l$^{-1}$ ($p < 0.0001$) and decreases in the haemoglobin difference concentration ($\Delta[Hbdiff] = [CCO]$ of 0.24 (0.06–0.28) μmol l$^{-1}$ ($p < 0.01$). These haemoglobin changes suggest a reduction in cerebral oxygen delivery despite an increase in cerebral blood volume, the latter presumably related to hypoxic cerebral vasodilatation. $\Delta ecDO_2$ correlated significantly with $\Delta[CCO]$ ($r = 0.78$, $p < 0.001$) but not with $\Delta[HbT]$ ($r = 0.33$, $p = 0.584$) or $\Delta[Hbdiff]$ ($r = 0.49$, $p = 0.145$), suggesting that $\Delta[CCO]$ might be a superior marker of reduced cellular oxygen availability than conventional haemoglobin-derived NIRS variables (figure 2).

We subsequently extended this work into the clinic and incorporated the broadband spectroscopy system into bedside multi-modal cerebral monitoring. In eight mechanically ventilated adult head-injured patients, cerebral microdialysis and broadband spectroscopy were added to the measurement of brain tissue oxygen tension to investigate the effects of normobaric hyperoxia on cellular and mitochondrial redox states assessed by the brain tissue lactate/pyruvate ratio and $\Delta[CCO]$, respectively [56]. Mean (range) brain tissue oxygen tension increased by 7.2 (4.5–9.6) kPa ($p < 0.0001$) during ventilation with 100 per cent oxygen, the lactate/pyruvate ratio decreased by 1.6 (1.0–2.3) ($p = 0.02$) and $\Delta[CCO]$ increased by 0.21(0.13 – 0.38) μmol l$^{-1}$ ($p = 0.0003$). $\Delta[CCO]$ correlated with changes in brain tissue oxygen tension ($r = 0.57$, $p = 0.005$) and in the lactate/pyruvate ratio ($r = −0.53$, $p = 0.006$). These changes are suggestive of hyperoxia-induced oxidation in cerebral cellular and mitochondrial redox states and are consistent with an increase in aerobic metabolism. Further studies that are powered to determine any potential outcome benefits of such improvements in cerebral metabolic state are warranted.

The challenges of measuring CCO using NIRS are substantial and particularly complex in the clinical setting. CCO is present in much lower concentrations in the tissue than oxy- and deoxyhaemoglobin and has an absorption spectrum overlapping that of these chromophores. The low signal-to-noise ratio also raises the question of whether the CCO signal contains sufficient information to be of clinical relevance. Furthermore, different algorithms produce markedly different results when analysing the same dataset, highlighting the unreliable nature of the CCO signal [7]. In an attempt to address these issues, we have recently developed a hybrid optical spectrometer comprising a novel combination of broadband and frequency-domain near-infrared systems. The hybrid optical spectrometer has been described in detail elsewhere but, in brief, comprises two identical broadband spectroscopy systems and a two-channel frequency-domain spectrometer capable...
Figure 3. Simultaneous measurement of changes in right frontal cortical brain tissue oxygen partial pressure (PbrO$_2$) (black) and cytochrome $c$ oxidase concentration ($\Delta$oxCCO) (grey), during a period of normobaric hyperoxia in a patient with diffuse axonal injury following a traumatic head injury. PbrO$_2$ was measured using a commercially available Clarke-type electrode (Licox, Integra Lifescience, Plainsboro, NJ, USA) and $\Delta$oxCCO using a custom-built hybrid optical spectrometer. (Adapted from A. Ghosh 2011, unpublished observations. Reproduced by permission.)

of absolute measurement of optical absorption and scattering at 690, 750, 790 and 850 nm over two regions of interest [57]. [HHb], [HbO$_2$] and [CCO] are calculated using the UCLn algorithm [7] by fitting changes in attenuation from 740 to 860 nm using a 35 mm source–detector separation. We have made some preliminary measurements with the hybrid optical spectrometer in healthy volunteers [58] and are currently collecting data in further volunteer studies and also in brain-injured patients. Figure 3 demonstrates changes in CCO during normobaric hyperoxia measured using the hybrid optical spectrometer in a patient with acute brain injury; complete data will be presented shortly.

6. Mathematical model-assisted data interpretation

NIRS and other multi-modal monitoring generates large and complex datasets whose interpretation is not always straightforward. Furthermore, what can be measurable at the bedside and what clinicians really need to know are often very different. As with the assessment of cerebrovascular autoregulation from information contained in the arterial blood pressure and intracranial pressure signals, clinically relevant information may be hidden within the signals of other commonly measured intracranial variables. Mathematical models of the cerebral circulation and energy metabolism have been developed that can be used to interpret multi-modal monitor-derived data and maximize their clinical
usefulness [59]. Such models produce new data streams, allowing the clinician to access simultaneously measured signals and model predictions of measured and unmeasured variables. Although the CCO signal has great potential as a marker of cellular oxygen metabolism, it is also the hardest to interpret. Combining measurement with modelling might allow information that is of potential clinical importance to be extracted [60]. Further validation of the model against in vivo data is required to determine whether it has potential to identify artefactual trends in the measured CCO signal and, importantly for clinical applications, to make predictions about cerebral blood flow and metabolism. A multi-modal physiological modelling approach integrating directly with the measurement of multiple physiological variables has enormous potential to deliver enhanced information that can be used to support clinical decision making in real time.

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