ORIGINAL RESEARCH

Ravi S. Samraj MD
Lara Nicolas MD

Division of Pediatric Critical Care, Shands Children's Hospital, UF Health, Gainesville, FL

Near infrared spectroscopy (NIRS) derived tissue oxygenation in critical illness

Abstract

Purpose: Near infrared spectroscopy (NIRS) is an emerging technology that can measure tissue oxygen saturation levels (StO_2) and has many potential clinical applications. NIRS devices have been studied in various disease states in the pediatric as well as adult populations. A review of this technology, with its potential applications and a review of current evidence is presented.

Principal findings: NIRS-derived regional tissue oxygen saturation (StO_2) is superior to pulse oximetry as it measures tissue oxygen saturation and reflects imbalance between oxygen supply and local demand. Becoming more widely available, it still does not have a firmly established role due to its technical limitations and to the lack of large multi-centric randomized controlled studies necessary to confirm its utility, cost-benefit effectiveness and role in improving patient outcomes.

Conclusion: Widespread availability, ease of use, non-invasive nature and continuous data display makes it an attractive option for bedside clinical monitoring.

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Correspondence to:
Ravi S Samraj MD, Assistant Professor
Pediatric Critical Care Medicine
Shands Children's Hospital, UF Health
1600 Archer Rd.
Gainesville, FL 32608
E-mail : ravisamraj@gmail.com

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Maintaining tissue perfusion and oxygenation is the cornerstone of therapy for patients with critical illnesses. An imbalance of oxygen delivery and tissue oxygen consumption leads to anaerobic metabolism, cellular injury and organ dysfunction and is associated with poor outcomes; consequently, monitoring tissue oxygen delivery and consumption status is of paramount importance in critically ill patients. Assessment of tissue oxygenation continues to be a challenge in clinical practice [1]. Routinely used bedside tools, including pulse oximetry, provide a continuous assessment of blood hemoglobin saturation levels; however, they do not estimate tissue oxygen demand/oxygen delivery imbalance. Blood lactate levels, acid-base status and central venous oxygen saturation levels reflect tissue metabolism; however, they are invasive tests and do not offer the advantage of continuous monitoring. Serial measurements of some of these tests (lactate) can be useful but they do not provide the advantage of continuous display at beside to the clinician necessary for real time monitoring and decision making. Until recently, only experimental invasive techniques (needle electrodes) were available to measure tissue oxygenation. Near infrared spectroscopy (NIRS) is a non-invasive optical technique that can be used to continuously monitor tissue oxygen delivery and oxygen consumption status. Initially developed as a research tool, it has been subsequently studied and used in clinical medicine in various pathophysiological states. We present the science behind NIRS, review the current evidence and highlight its potential applications.

Results

Near infrared spectroscopy (NIRS) technology

NIRS uses a modified Beer-Lambert Law for measurement of concentration of a substance according to the absorption and scattering of light. Visible light penetrates tissues for only short distances; however, NIRS devices use near infrared light (an optical window of 700–900 nm) that passes through skin or bone into underlying tissue. Because oxy-hemoglobin, deoxy-hemoglobin and cytochrome aa3 possess distinct absorption characteristics in the near infrared spectrum, hemoglobin-O_2 saturation can be calculated. In contrast to pulse oximetry, which detects the arterial pulse signal, NIRS devices detect total light signal. Because most of the blood is in capillaries and veins and not in arteries, quantitatively the greatest contribution to the absorption spectrum of hemoglobin in NIRS is derived from venous-weighted capillary blood. Some newer devices use a dual detector system to subtract absorbances attributed to a shallow light path from those from a deeper light path. The device displays an approximation of venous-weighted hemoglobin saturation in tissues deep to the sensor [2]. Values derived from the algorithm are displayed on the monitor as a relative number from 0% to 100%.

Correlation with tissue oxygenation

NIRS-derived StO_2 is an indirect marker of central venous oxygenation. NIRS-derived regional tissue oxygen saturation (StO_2) has been shown to correlate with capillary–venous hemoglobin saturation [3]. Studies have also shown that NIRS-derived cerebral StO_2 correlates with jugular bulb venous saturation (SjO_2) as well as with central venous oxygen saturation ($ScvO_2$) [4-7]. In contrast, a pediatric study showed that cerebral StO_2 correlated better with $ScvO_2$ than with SjO_2 but did not reliably estimate the change in either measurement; however, this was a study of a heterogeneous group of patients in different clinical settings [8]. Other studies have shown that despite significant correlation with SjO_2, sensitivity is poor and may not be reliable. StO_2 measures regional tissue oxygen delivery and oxygen consumption status while $ScvO_2$ evaluates the adequacy of oxygen delivery and oxygen consumption status in the whole body; hence, some authours opine that these cannot be compared with one another and should probably be used in combination in clinical practice [10, 11].

NIRS monitoring devices

NIRS devices consist of an optical probe, which is placed on the patient, and a monitor. NIRS can be used to monitor either the cerebral or somatic circulation. For cerebral NIRS monitoring, the probe should be placed on the left or right side of the forehead. The probe should not be placed over hair, sinus cavities, superior sagittal sinus and subdural or epidural hematomas as it may lead to inaccurate readings. For somatic NIRS monitoring, the probe is placed over the circulatory area of interest (Table 2). The probe is connected via a cable to a monitor, which displays real time cerebral or somatic StO_2 data (Figure 1).

Real time data monitoring

The NIRS device can provide real time assessment of tissue perfusion, in response to various insults or interventions. Real time data display helps the clinician to assess the response to interventions such as resuscitation, inotropic support, ventilator support and blood transfusions (Figure 2).

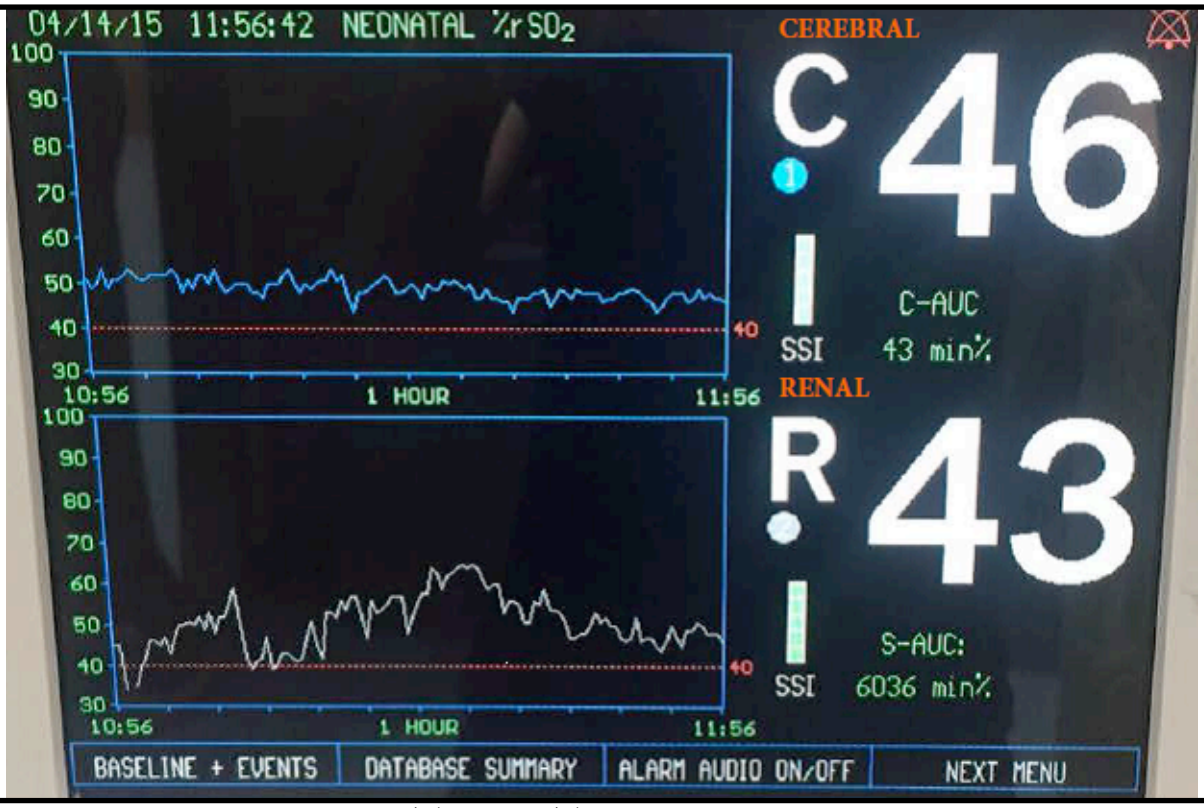

FIGURE 1. NIRS device monitor showing cerebral (C) and renal (R) StO_2 trends over 1 hour.

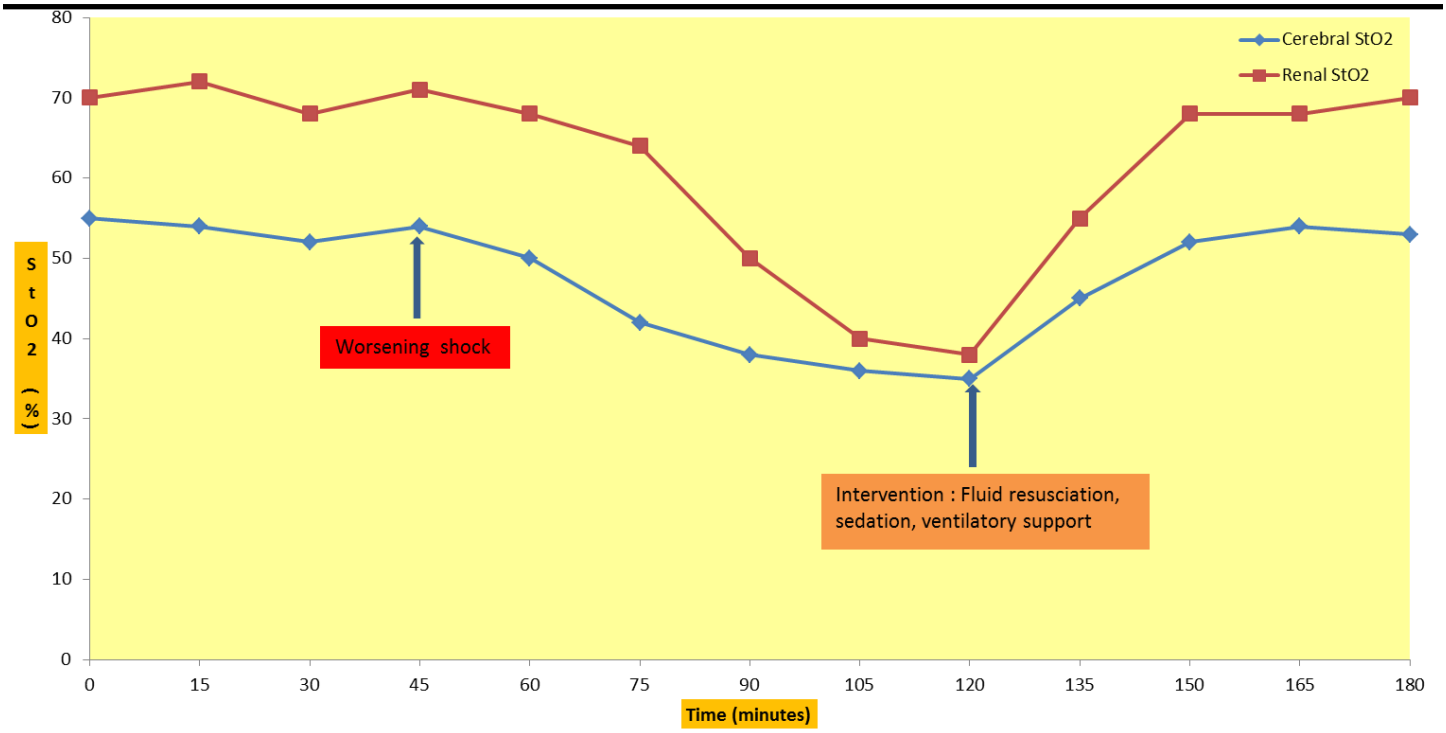

FIGURE 2.Illustration showing progressive decline in renal and cerebral StO_2 in patients exhibiting shock, and improvement with appropriate intervention.

Regional circulatory system imbalance and multi-site NIRS monitoring

Cerebral tissue has a high oxygen extraction ratio; consequently, the cerebral StO_2 value is lower than renal StO_2 value, which has a high blood flow but low extraction ratio. At the bedside, this translates to cerebral StO_2 measurements of 60-80% under normal conditions and a higher renal/splanchnic measurement of 65-90% [12, 13].

Obtaining the cerebral and somatic oxygenation levels simultaneously is valuable to help in clinical decision making. A (somatic–cerebral) StO_2 difference has been shown to predict post-operative complications, biochemical shock and mortality [14]. In a study of 79 neonates with hypoplastic left heart syndrome, a (somatic–cerebral) StO_2 difference of <10 in first 48 postoperative hours after stage 1 palliation was associated with an increased risk of biochemical shock and post-operative complications while a (somatic–cerebral) StO_2 difference of zero or less was associated with increased risk of mortality [14]. In another neonatal study, the ratio of cerebral and splanchnic StO_2 (termed cerebro-splanchnic oxygenation ratio; CSOR) was shown to have 90% sensitivity in detecting splanchnic ischemia [15]. This ischemia can be identified by continuous multisite NIRS monitoring and may provide a therapeutic window to prevent end organ injury and change the course of the disease.

Potential applications of NIRS

Non-invasive monitoring of tissue hemoglobin oxygenation can be done, in real time [16]. NIRS has the advantage of providing continuous bedside monitoring of both cerebral and somatic circulation [16, 17]. Cerebral regional NIRS monitoring gives an indication of adequacy of cerebral blood flow and perfusion [18, 19], whereas somatic regional NIRS monitoring provides information regarding perfusion to vulnerable organs. Both cerebral and somatic NIRS may help in hemodynamic management and potentially improve outcomes by early detection of organ dysfunction and in preventing further damage by early institution of therapy [20]. Renal and splanchnic oxygenation are parts of the somatic circulation that have been mostly measured in clinical practice using NIRS [21]. Monitoring using NIRS has been reported in the pediatric as well as the adult population [21-23] and may provide useful data in various pathophysiological states (low cardiac output, sepsis, trauma, post-surgical state and necrotizing enterocolitis). Utility of this technology has been studied both in cardiac and non-cardiac population [12, 16, 24, 25]. In addition, use of the NIRS device is associated with a lower likelihood of instituting unnecessary pre-operative therapies (e.g., mechanical ventilation) [26]. NIRS devices have been used in a wide variety of clinical applications (Table 1).

TABLE 1. Clinical applications of StO_2 monitoring

Clinical applications
Non-invasive monitoring of cardiac output
Non-invasive monitoring of cerebral perfusion
Early recognition of shock (sepsis, trauma)
Assessment of response to therapy
Early detection of NEC (necrotizing enterocolitis)
Prognostication
Neurodevelopmental outcome prediction

Cardiac surgery

NIRS monitoring has been studied in infants and children after surgery for congenital heart disease. In this population, studies have shown a strong correlation between splanchnic StO_2 and central venous oxygen saturation ($ScvO_2$) [27]. In addition, there is good correlation between cerebral or renal StO_2 of less than 65% and hyperlactemia (>3 mmol/L) in the first 24 hours after cardiac surgery in neonates [28]. A low somatic StO_2-cerebral StO_2 difference predicted shock, anaerobic metabolism and a longer intensive care unit stay [14, 29]. Although inter-patient variability was high, within-patient trending of SvO_2 by two-site NIRS showed a close correlation [25]. Cerebral StO_2 measurements have also shown to be beneficial during cardiac catheterization in children with congenital heart disease. It can aid in assessment of brain perfusion, as well as airway stability [22]. Jugular venous bulb saturation is a marker of cerebral saturation, and cerebral StO_2 has been shown to correlate with jugular venous bulb saturation [30]. In a cohort of 200 adult patients undergoing coronary artery bypass graft surgery, a randomized control study showed that using an interventional algorithm based on cerebral StO_2 readings resulted in significantly fewer major complications (death, stroke, renal and respiratory failure) and a shorter length of stay (LOS) in the intensive care unit [31]. Similar findings were reported in a cohort of 2000 cardiac surgical patients with a decrease in the incidence of major complications, especially stroke [32]. In addition to cerebral NIRS monitoring, renal StO_2 monitoring has been shown to be helpful in detecting early renal dysfunction in infants undergoing cardiac surgery. This is particularly important for identifying potential kidney

dysfunction and intervening to prevent progression to organ damage [33]. During cardiopulmonary bypass, thenar muscle StO_2 decline preceded peak lactate levels by a significant period of time (93 min) [34]. It appears that NIRS monitoring may have a role to play in the peri-operative period by helping to assess adequacy of cerebral circulation; however, not all studies showed this correlation. A recent study of pediatric cardiac surgery patients did not find a good correlation between regional oxygen saturation of brain/kidney and $ScvO_2$ [35]; however, the authors did mention that NIRS-derived data may still provide useful information regarding regional circulation.

Neuroprotection

Intra-operative cerebral injury is a major cause of malpractice claims [36]. The brain is susceptible to ischemic insult, due either to impairment of cerebrovascular auto-regulation or to poor cerebral blood flow. Cerebral NIRS monitoring can potentially be used to protect the brain under both these conditions. The ease of obtaining cerebral StO_2 measurements makes it an attractive option for monitoring. In animal models, cerebral StO_2 <40% was associated with intracellular anaerobic metabolism and depletion of high-energy phosphates [37]. Clinical data in children and adults support the hypothesis that cerebral StO_2 values less than 40% for 10 mins, a change in baseline of more than 20%, or a nadir of below 35%, are associated with hypoxic-ischemic neural injury [38-42]. Cerebral StO_2 has also been demonstrated to be useful in detecting cerebral hypo-perfusion during carotid end arterectomy under general anesthesia [43]. Prolonged intra-operative cerebral desaturations are associated with adverse neurological outcomes and prolonged hospital stay. Furthermore, interventions carried out by thoughtful use of the cerebral oximeter are associated with significant reduction in neurologic injury, organ dysfunction and mortality [44]. The use of NIRS is becoming popular for ensuring neuro-protection after cardiac surgery in adults [45] and the use of NIRS to tailor peri-operative physiologic management has been shown to result in improved patient outcomes [46].

In the neonatal population, NIRS has been used to show changes in brain oxygenation during brain cooling after birth asphyxia [47]. A recent systematic review found that reductions in cerebral StO_2 may identify cardiopulmonary bypass cannula malposition [48]; however, they found only low level evidence between low StO_2 and postoperative neurologic complications. A review on cerebral oximetry published in 2009 identified nine studies evaluating the use of NIRS in surgery (cardiovascular surgery, liver transplant and abdominal surgery). The authours noted that eight of these nine studies support the use of cerebral oximetry [49].

TABLE 2. NIRS probe placement

NIRS	Location of probe
Renal	Latissimus dorsi, posterior flank, T10-L2 vertebrae, paramedian position
Splanchnic	Lower abdomen, external oblique muscle
Cerebral	Frontal bone, supraorbital paramedian position
Muscular	Pectoralis (chest), over brachioradialis (forearm), biceps (upper arm), thenar (palm) or gastrocnemius (calf) muscle

Impaired CBF autoregulation occurs in 20% of patients during CPB [50]. There is no gold standard for measuring cerebral blood flow to determine autoregulation. Transcranial Doppler (TCD) sonography, electroencephalogram and jugular venous bulb oximetry are other modes of cerebral perfusion monitoring [49]. Cerebral blood flow monitoring with TCD-measured blood flow velocity has been validated in volunteers and patients with trauma and cardiac surgery [18, 51]; however, this technique is cumbersome and needs special expertise. NIRS technology has been shown to be useful for monitoring cerebral autoregulation and can act as a surrogate for cerebral blood flow [18, 19, 52]. Targeting arterial blood pressure, based on cerebral blood flow autoregulation monitoring, may provide a way to prevent cerebral hypo-perfusion or other organ injury. Patients with impaired cerebral autoregulation during cardiopulmonary bypass were found to have a higher incidence of postoperative stroke [50]. Renal injury has been shown to be associated with excursions of mean arterial blood pressure below the limit of autoregulation [53]. Recently, a moving linear correlation coefficient between arterial blood pressure and cerebral StO_2 (termed cerebral oximetry index; Cox), obtained using a prototype NIRS monitor, was found to have good correlation and agreement with TCD-derived mean velocity index in cardiac surgery patients [54]. Use of this technology could allow cerebral blood flow autoregulation monitoring as a means of individualizing arterial blood pressure targets during cardiac surgery [54]. Cerebral NIRS monitoring, though useful in various situations, has the disadvantage of representing only regional cerebral perfusion; i.e., the area under the NIRS probe. It may not give a true estimate of global cerebral blood flow in situations with heterogeneous blood flow distribution, as occurs in localized brain trauma. Cerebral oxygenation monitoring using NIRS is currently the

subject of intense research, both in the adult and in pediatric populations.

NIRS in septic shock

The systemic inflammatory response to sepsis may cause impaired tissue oxygenation, which can persist despite restoration of normal hemodynamics and systemic oxygen transport, and which results in high mortality and morbidity. Monitoring tissue oxygen saturation using NIRS in patients with sepsis can be beneficial through early recognition of tissue hypoxia. Cerebral and somatic NIRS monitoring have been used in patients with sepsis/septic shock and studies have shown correlation with invasive monitoring techniques [23].

Studies have showed significant differences in thenar tissue oxygen saturation between patients with severe sepsis and healthy controls [16]. NIRS-derived measurements have been used to predict mortality due to sepsis [55, 56]. Specifically, it was shown that thenar muscle StO_2 measurments less than 60% were common in a cohort of adult ICU patients and was associated with poor outcomes [57]. A thenar muscle StO_2 cut-off value of 75% has been proposed as a specific, rapid, non-invasive first step for detecting patients with low $ScvO_2$ levels [58]; however, other studies have yielded less encouraging results. In a cohort of 168 adult patients treated for sepsis in the emergency room, mean baseline thenar muscle StO_2 levels were not different between patients with shock and controls. This study found significant correlation between occlusion and recovery StO_2 slopes (obtained using a vascular occlusion technique) and SOFA (Sequential Organ Failure Assessment) scores [59]. In another study of 49 adult patients treated for septic shock in the emergency room, initial thenar muscle StO_2 did not differentiate between survivors and non-survivors; however, a significant increase in StO_2 was found after treatment in survivors [60]. Large multi-centric trials evaluating the various components of thenar muscle StO_2 (initial, response to therapy, occlusion and recovery slope) are needed to demonstrate its usefulness in septic adult patients. The utility of StO_2 monitoring in the pediatric septic patients has not been well studied.

Vascular Occlusion Test (VOT)

Sepsis is associated with microcirculatory changes, which include increased capillary permeability, decreased oxygen diffusion and altered regional vasoregulation [61-63]. VOT is a dynamic test that studies the changes in microcirculation and thenar muscle oxygen saturation, in response to a transient ischemic challenge. VOT is performed as follows: obtain a baseline thenar StO_2 value at rest, and then inflate the upper extremity blood pressure cuff to 30 mmHg above the patient's systolic blood pressure, keep cuff inflated until StO_2 decreases to 40% and then rapidly deflate the cuff. Thenar StO_2 response is followed until StO_2 returns to baseline. During the test, the thenar StO_2 deoxygenation slope (DeOx) and thenar StO_2 reoxygenation slope (ReOx) are obtained and represented as changes in O_2 saturation in percentage over time [64]. In other studies, the upper extremity blood pressure cuff was inflated to 50 mmHg greater than the patient's systolic blood pressure and the inflation was sustained for 3 minutes before deflation [65]. Studies utilizing the VOT have shown that it improves the predictive value of thenar StO_2 in patients with septic shock [65, 66]. Furthermore, the DeOx slope during VOT has been shown to have a significant correlation with $ScvO_2$ and correlated with peripheral vascular resistance while the ReOx slope significantly correlated with mean arterial blood pressure [64]. Another study in patients with severe sepsis and organ dysfunction found that the thenar StO_2 value at baseline and throughout ischemia was similar compared to healthy control subjects; however, the rate of rise of thenar StO_2 post-ischemia resaturation time was significantly impaired in septic subjects with severe organ dysfunction compared with controls [67]. Similar results were found in another study involving critically ill septic patients: there was no difference in baseline thenar StO_2 or StO_2 desaturation during ischemic period; however the post-ischemia resaturation time was significantly longer in patients with sepsis compared with healthy controls [68]. VOT testing during ICU stay has shown that improvements in thenar StO_2 deoxygenation rates were correlated with survival and sequential organ failure assessment (SOFA) scores [69]. Other studies have looked at the effect of novel therapies in sepsis and their effect on thenar StO_2. VOT has shown that the administration of activated protein C in septic patients was associated with improvement in muscle oxygenation as well as reperfusion [70]. VOT may be of use to the clinician taking care of critically ill patients; however, further large scale studies are needed. The exact underlying pathophysiological mechanism and the microcirculatory changes in patients with sepsis and how these affect thenar tissue deoxygenation and subsequent reoxygenation as well as the effect of external factors (medication and ventilation) are not well elucidated and need to be further studied.

NIRS in trauma

NIRS have been used to evaluate outcomes of trauma and have been shown to detect early changes in perfusion, while blood pressure is still being maintained. In the early stages of shock,

cutaneous and muscular blood flows are diverted to vital organs (brain, heart, kidney and liver). During this phase, NIRS devices may detect a fall in tissue oxygen levels, thus helping in early shock recognition. A prospective observational study of 707 patients showed that thenar muscle StO_2 levels discriminated between patients without shock and patients with severe shock. [24]. A low NIRS measurement in early trauma is associated with an increased risk of multi-organ dysfunction and mortality [71, 72]. Cerebral oxygen saturation and calf muscle oxygen saturation were reported to correlate well with acute blood loss in a cohort of 40 adult patients donating blood [73]. Cerebral StO_2 values less than 60% for longer periods after traumatic brain injury were associated with higher mortality, intracranial hypertension and compromised cerebral perfusion [74] and were moderately accurate at predicting severe brain hypoxia (brain tissue oxygen tension, $PbtO_2$ =12-15 mmHg). Thenar NIRS monitoring can predict mortality and can help to differentiate survivors and non-survivors [75].

NIRS in assessing splanchnic circulation

A study in the neonatal population showed that a lower somatic/cerebral NIRS ratio of <0.75 was associated with eight times greater risk of developing necrotizing enterocolitis (NEC) [76, 77]. Assessing the splanchnic circulation is easier in neonates and young infants due to the paucity of fat; however, this technology may not yield reliable values beyond this age group.

Long-term outcomes

Prolonged low cerebral StO_2 is associated with new or worsened lesions on MRI; typically, white matter changes in patients after congenital heart surgery [78]. Lower psychomotor performance score (Bayley scale) have been reported in infants with biventricular repair who had low cerebral StO_2 up to 60 mins after separation from cardiopulmonary bypass [79]; however, not all studies found NIRS monitoring improved long-term outcomes. A study of 47 adult patients undergoing coronary artery bypass grafting with cardiopulmonary bypass concluded that cerebral StO_2 value of less than 40%, a decrease of more than 25% or a longer duration at a lower value did not predict postoperative cognitive performance [80]. The role of cerebral StO_2 monitoring on long-term neurological outcomes is not clear and needs to be further studied.

Limitations

NIRS, though a potentially useful bedside tool for non-invasive monitoring of StO_2, has limitations. Some of these limitations are due to the lack of standardization of NIRS devices and some to patient-related factors (Table 3). NIRS StO_2 is a reflection of the tissue oxygen delivery and oxygen consumption status of the tissue under the probe, which may be different from the systemic oxygen delivery-consumption balance. This can be seen in focal brain trauma, where the tissue damage and edema may result in less perfusion and consequently lower cerebral StO_2, thus not reflecting global brain oxygen delivery-consumption status of the whole body. Skin

TABLE 3. Limitations of StO_2 monitoring

Limitations
Different optical probes, sensors and algorithms in commercial devices
Cost-benefit analysis not proven (1)
Absence of thresholds for normative data (4)
Research difficult due to lack of standardization across devices
NIRS derived value represents only area under the probe
False values (previous stroke, scar, brain malformation etc.)
Source of discomfort (children)
Not reliable with increase in subcutaneous tissue (fat, hematoma, edema)
Polycythemia (64)
Inter- and intra-individual variability
Agitation/muscular activity yield falsely low values

pigmentation and myoglobin can also interfere with NIRS measurments. Myoglobin is not an issue with cerebral StO_2 monitoring due to minimal muscle in region of NIRS probe placement; however, it can affect values while studying regional muscle oxygenation, resulting in unreliable values. Other patient-related factors affecting the NIRS-derived values include patient agitation, skin conditions (burn, infection or scar), brain malformation, polycythemia and subcutaneous fat. Consequently, obtained values should be interpreted carefully in the context of the given clinical situation. High cost, especially for the single use sensor, further limits the widespread use of NIRS - especially in the absence of cost-benefit evidence. Finally, NIRS derived values can be significantly influenced by variations in regional circulation.

Conclusions

NIRS technology allows determination of regional oxygen saturation levels across different circulatory beds and has potential applications for various clinical conditions. NIRS's non-invasive nature and it's ability to continuously monitor organ perfusion status make it a useful bedside tool for the clinician. Becoming more widely available, it still does not have a firmly established role due to its technical limitations and to the lack of large multi-centric randomized controlled studies necessary to confirm its utility, cost-benefit effectiveness and role in improving patient outcomes.

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