European Society for Paediatric Research
Society for Pediatric Research
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SPECIAL ARTICLE

Near-infrared spectroscopy for perioperative assessment and neonatal interventions

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Perioperative applications of near-infrared spectroscopy (NIRS) to monitor regional tissue oxygenation and perfusion in cardiac and noncardiac surgery are of increasing interest in neonatal care. Complex neonatal surgery can impair adequate oxygen delivery and tissue oxygen consumption and increase the risk of neurodevelopmental delay. Coupled with conventional techniques, NIRS monitoring may enable targeted hemodynamic management of the circulation in both cardiac and noncardiac surgical procedures. In this narrative review, we discuss the application of perioperative NIRS in specific neonatal interventions, including surgical intervention for congenital heart defects, definitive closure of the patent ductus arteriosus, neurological and gastrointestinal disorders, and use of extracorporeal membrane oxygenation. We identified areas for future research within disease-specific indications and offer a roadmap to aid in developing evidence-based targeted diagnostic and management strategies in neonates.

Pediatric Research; https://doi.org/10.1038/s41390-021-01791-1

IMPACT: There is growing recognition that perioperative NIRS monitoring, used in conjunction with conventional monitoring, may provide critical hemodynamic information that either complements clinical impressions or delivers novel physiologic insight into the neonatal circulatory and perfusion pathways.

INTRODUCTION

Perioperative applications of near-infrared spectroscopy (NIRS) in cardiac and noncardiac surgery are of increasing interest in neonatal care. Neonates, particularly those born preterm, face multifaceted adaptive processes that can predispose their developing organs to significant perioperative circulatory compromise. For example, both cardiac and noncardiac neonatal surgery can increase the risk of neurodevelopmental delay[1–3] and monitoring cerebral oxygenation may be critical to maintaining a stable cerebrovascular hemodynamic milieu. We have described the technology, reviewed the variability of the sensors, equipment, post processing, and interpretation of the NIRS data elsewhere.[4–7] NIRS is a noninvasive way to monitor tissue oxygen supply and consumption by continuously utilizing absorption properties of oxyhemoglobin and deoxyhemoglobin to characterize oxygenation and perfusion in regions of interest, including the brain, peripheral muscle, splanchnic, and/or kidney. With an ultimate goal of ensuring normal cellular metabolism during procedures, maintaining regional tissue blood flow and organ perfusion is crucial for limiting postoperative complications such as acute kidney failure, wound infection, and cognitive dysfunction in both cardiac and noncardiac surgery.

Perioperative NIRS can serve as a complementary hemodynamic monitoring tool and potentially aid in characterizing factors associated with the etiology and timing of potential adverse hemodynamic responses in cardiac and noncardiac neonatal surgical patients. The integration of hemodynamic information obtained by NIRS relevant to the perioperative clinical state may eventually provide a vehicle for which to devise a diagnostic impression, determine a pathophysiological choice for support, and evaluate the response to therapeutic intervention as related to clinical outcomes. In combination with conventional hemodynamic monitoring, NIRS may complement what is clinically suspected or deliver unique physiologic insight into circulatory pathways. This narrative review focuses on the role of perioperative NIRS with specific neonatal surgical interventions, including congenital heart defects (CHD), definitive closure of the patent ductus arteriosus (PDA), neurological and gastrointestinal disorders, and use of extracorporeal membrane oxygenation (ECMO) (Fig. 1). Contemporary reports related to routine clinical

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Received: 7 May 2021 Revised: 14 September 2021 Accepted: 17 September 2021
Published online: 29 October 2021

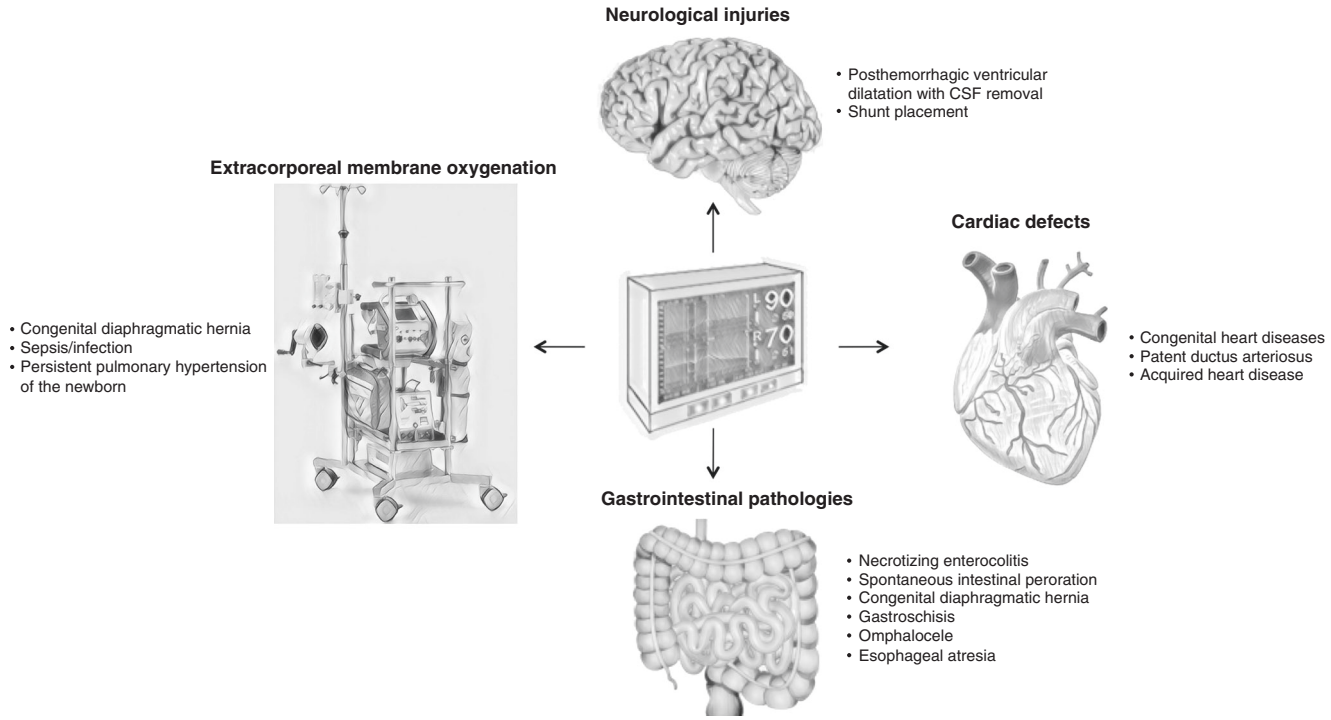

Fig. 1 Selected application of near-infared spectroscopy for perioperative assessement and neonatal interventions

assessment and care in each situation, ongoing challenges, and recommendations for research opportunities are presented. We identify gaps in knowledge, provide a summary of research priorities (Table 1), and recommend a diagnostic approach for the use of perioperative NIRS in neonates.

CARDIAC DEFECTS

Congenital heart disease

Advances in neonatal, cardiac, and cardiothoracic surgical management continue to improve outcomes for neonates with CHD. However, severe neonatal morbidities (e.g., intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC)) occur in this population, prompting a renewed focus on neurodevelopmental prognosis as a research priority for providers. Altered cerebral blood flow (CBF) patterns with various types of CHD have been identified by magnetic resonance imaging studies,[8] and NIRS use in this high-risk population may help identify perturbations that result from regional perfusion and cause ischemia. With CHD, perioperative evaluation of cerebral regional tissue oxygenation ($rStO_2$) focuses on maintaining CBF as an addition to the assessment of cardiac stroke volume, central venous oxygen saturation, mean arterial pressure, arterial hemoglobin O_2 saturation, and arterial carbon dioxide pressure. In CHD and other perioperative situations, $rStO_2$ is used to calculate the fractional tissue oxygen extraction (FTOE). However, it is important to acknowledge differences in cerebral hemodynamics and oxygen metabolism according to the pathophysiology of specific cardiac defects.[9] Perioperative cerebral NIRS monitoring evaluates brain oxygenation both pre- and post surgery, while intraoperative monitoring can assist anesthesiologists and surgeons in optimizing cerebral oxygenation during procedures to protect the neonatal brain.[10]

NIRS monitoring across the continuum of the perioperative (preoperative, intraoperative, and postoperative) CHD period enhances the ability to predict neurodevelopmental disabilities, as brain injury in these infants may occur at any time during the clinical course.[11] NIRS reference values for cerebral oxygenation during transitional circulation in infants with CHD and ductal-dependent pulmonary or systemic circulation are available,[12] but are lacking during the subsequent perioperative phases. Furthermore, a recent narrative review provides the normative and critical values of cerebral and somatic tissue oxygen saturation and the interpretation of these values, along with the clinical studies of NIRS as a perioperative monitoring modality in the pediatric congenital heart disease population.[13]

There have been no randomized clinical trials conducted in infants with CHD, and until such time it remains unclear if interventions based on $rStO_2$ and FTOE will have actual benefits on clinical outcomes. During surgical repair of CHD, cerebral NIRS can detect episodes of cerebral hypoxia more reliably than arterial SpO_2 monitoring.[14, 15] Hypoxia–ischemia is recognized as an important determinant of acquired brain injury and knowledge about brain perfusion-oxygenation starting at birth and tracking through each perioperative phase may be beneficial to formulate management strategies. The predictive value of perioperative NIRS for neurodevelopmental outcomes after cardiac surgery in infancy has also been investigated.[16] Infants with ductal-dependent circulation show significantly lower $rStO_2$ than controls immediately after birth.[12] In infants with transposition of great arteries[17] or single ventricle palliative surgery,[18] time to surgery correlated with increased acquired white matter damage; negative and positive linear trends in $rStO_2$ and cerebral FTOE were observed, respectively, that could potentially explain the observed increase in brain damage.[18, 19]

Hemodynamic perioperative care of infants with CHD focuses on actions to optimize contractility, improve diastolic function, and reduce afterload. Perioperative $rStO_2$ trending can potentially be deployed toward appropriate intra- and postoperative treatment of patients with desaturations surpassing defined thresholds. Systematic assessment on the effect of inodilators during the perioperative period used to treat or prevent postoperative low cardiac output syndrome (LCOS) has documented improved cerebral and systemic oxygenation both in observational studies[20] and randomized clinical trials.[21] NIRS monitoring during pediatric

Table 1. Current knowledge gaps, research opportunities, and priorities for utilization of perioperative NIRS.

Section and focus areas	Key barriers and challenges	Research opportunities and priorities
Congenital heart disease	Lack of understanding if the application of NIRS monitoring can increase survival of target population (especially preterm born infants).	Establish a dedicated research consortium and a task force to assemble these data with standardized protocols in a reference registry
	Heterogeneity of the pathophysiology of congenital heart defects	Promote noninvasive-multichannel (variety of parameters) continuous monitoring to characterize abnormal patterns at any time during the clinical course
	High prevalence of genetic and syndromic disorders associated with congenital heart lesions that can impact cerebral hemodynamics	Population studies to investigate the competing effects of CHD and phenotypic syndromes and genetic variability on cerebral hemodynamics
Neurosurgical	Lack of cut-off thresholds for $rStO_2$ and FTOE to guide intervention for removal of CSF fluids	Design large prospective cohorts of infants to determine the optimal timing of intervention, frequency, and CSF volume required to be drained based on NIRS-derived cerebral hemodynamics
	Paucity of standardized correlation of continuous NIRS measurements with other noninvasive circulatory parameters (e.g., mean arterial blood pressure, cardiac output, arterial distensibility)	Investigate noninvasive multimodality simultaneous hemodynamic imaging approaches to link cerebral autoregulation, cerebral oxygenation, and oxygen metabolism with cardiopulmonary parameters
	Impact of sources of error with optical neuromonitoring (e.g., signal contamination with motion artifact and ambient light) and scalp integrity still exist with different cohorts	Define mandatory, recommended, and research approaches to assess how to account for all sources of errors with prospective analysis
Patent ductus arteriosus	Lack of homogeneity/standardization in NIRS-derived measures for an indication for definitive (surgical or transcatheter) closure	Design longer, time-to-event clinical trials to validate potential NIRS-based endpoints that provide real-time estimates of cerebral hemodynamics for definitive closure of the PDA
	Reduction in treatment/ligation frequency (less proactive therapeutic approach) may limit the number of potential participants in future studies	Prospective clinical studies that investigate the changes in loading conditions on cerebral hemodynamics with a focus on the impact of low cardiac output syndrome
	Poor understanding of the associating between systemic hemodynamic parameters and serial NIRS-derived measures $rStO_2$, FTOE, and DCS-derived CBF and $CMRO_2$	Combine FDNIRS-DCS monitoring with multimodality systemic hemodynamics that may include echocardiography and other noninvasive measures of cardiac output, systemic vascular resistance, and stroke volume
Gastrointestinal	Uncertainty regarding which babies and which specific gastrointestinal conditions would benefit most from NIRS monitoring	Determine whether single-organ vs. multiple-organ monitoring through a randomized control trial design provides added value for patient management and overall outcomes
	Uncertainty regarding the impact of feeding patterns, breast milk vs. formula, and stool content (meconium vs. transitional stool) on NIRS absorption properties and signal integrity	Develop approaches that can account for baseline variability of abdominal NIRS monitoring with correction factors that can be clinically applied in neonates to provide accurate and sensitive regional tissue oxygenation parameters
	Lack of standards regarding study design, data collection, analysis, and interpretation with link to long-term outcomes following intestinal perturbations in neonates	Establish large-scale prospective studies in healthy controls and neonates with abdominal pathology that include region-specific baseline variability
ECMO	Preemptive neurocritical monitoring in neonatal ECMO patients is still underutilized	Definition of cerebral biomarkers to be used in the selection of patients for ECMO or titration of this treatment
	Sparse evidence is available on the utility of NIRS during ECMO	Demonstrate the clinical benefit of NIRS monitoring in specific scenarios during neonatal ECMO
	Lack of confirmatory data that monitoring with NIRS can change the neurological outcome of ECMO newborns	Investigate the effect of specific ECMO-treatable diseases on cerebral oxygenation and neurodevelopmental outcome

NIRS near-infrared spectroscopy, *ECMO* extracorporeal membrane oxygenation, *$rStO_2$* regional tissue oxygenation, *CBF* cerebral blood flow, *FTOE* fractional tissue oxygen extraction, *CSF* cerebrospinal fluid, *$CMRO_2$* cerebral metabolic rate of oxygen, *FDNIRS-DCS* frequency-domain NIRS and diffuse correlation spectroscopy.

cardiac surgery has also been shown to improve intraoperative transfusion management, with $rStO_2$ guiding earlier transfusion, but with reduced total red blood cell (RBC) volume, and decreased the length of ICU stay.[22] In a small but impactful study during cardiopulmonary bypass, cerebral oxygenation assessment by NIRS was shown to reflect changes in temperature, perfusion pressure, hemoglobin content and central venous pressure, and may serve as a monitoring device for the neuroprotective optimization of these vital parameters.[23]

During cardiac surgery, a percent $rStO_2$ decrease from baseline (following anesthesia induction) below 52% was associated with receptive communication delay, whereas a postoperative $rStO_2$ nadir below 56% properly identified 100% of infants with cognitive delay.[16] Similar postoperative thresholds for cerebral oxygenation have been documented following single ventricle stage 1 repair in infants who later developed abnormal visual–motor integration capacity.[24] However, associations between lower cerebral hypoxia thresholds and postoperative

Table 2. Changes of cerebral oxygenation with surgical ligation of the patent ductus arteriosus closure.

First author (year)	*N*	GA (weeks)	BW (g)	Age (days)	Δ $rStO_2$ (%)	Δ FTOE	Time points	
							Before	After
Short term[a]								
Zaramella (2006)	16	27 (25–28)	895 (819–1315)	13 (11–20)	−4.5	NR	35 min	14 min
					−5.3	+0.05		27 min
Hüning (2008)	10	24 (23–27*)	748 (590–1070*)	14 (12–22*)	−6.0	+0.05	5–10 min	0–2 min
					−5.0	+0.04		2–5 min
					−2.0	+0.01		5–10 min
Vanderhaegen (2008)	12	27 (24–32*)	988 (555–1855*)	33 (6–88*)	+2.9	−0.015	5–0 min	0–5 min
					−3.1	−0.021	65–20 min	20–65 min
Kooi (2020)	9	26 (25–28*)	800 (640–960*)	18 days (14–30*)	−0.8	NR	4 h	0–4 h
Sum	47	Weighted mean			−2.8	+0.024		
Medium/long term[b]								
Lemmers (2010)	20	27 (25–30*)	907 (630–1540*)	7 (4–39*)	+8.0	−0.09	NR	24 h
Chock (2011)	12	26 (1)	841 (159)	16 (9)	+9.0	NS	NR	4–24 h
MacLaren (2016)	11	28 (27–30)	1022 (898–1146**)	29 days (25–33**)	+2.0	−0.02	4 h	24 h
Kooi (2020)	9	26 (25–28*)	800 (640–960*)	18 days (14–30*)	+2.8	NR	4 h	4–8 h
					+4.3	NR		8–12 h
Sum	52	Weighted mean			+6.2	−0.065		

Data are presented as median (interquartile range or range* or 95%CI**) or mean (standard deviation).
Cerebral $rStO_2$ data are presented irrespective of the different vendor approaches for reporting regional tissue oxygenation parameters. Short-term effects utilized Hamamatsu Photonics (Hamamatsu, Japan), except for Kooi et al. Medium-term effects utilized INVOS 4100 or 5100, Medtronic (Minneapolis, MN, USA). Although these technologies provide slightly different measures of $rStO_2$, their absolute values are comparable.[27] In addition, if FTOE data were not reported in a particular study, group means were estimated from the $rStO_2$ and SpO_2 data.[28]
NS not significant, *min* minutes, *NR* not recorded, *Δ $rStO_2$* changes of regional cerebral tissue oxygen saturation, *FTOE* fraction of tissue oxygen extraction (pre-/postsurgical PDA closure presented delta values between different time points in relation to the moment of clipping or start of surgical intervention).
[a]Short term refers to change in cerebral oxygenation values from before ligation to 0–4 h after ligation.
[b]Medium/long term refers to change in cerebral oxygenation values from before ligation to 4–24 h after ligation.

development of structural white matter damage are not consistent.[25, 26] Combined $rStO_2$ (cut-off value <58%) and lactate (cut-off value >7.4 mmol/L) at 24 h postoperative predict survival and neurodevelopmental outcome in infants with CHD undergoing surgical repair in the neonatal period.[27] Finally, early detection of postoperative low cardiac output has been accomplished by systematic assessment of intraoperative $rStO_2$ desaturation score (calculated by multiplying the rSO_2 below 50% by time (in s) (as AUC 1/4 area under the curve).[28] In summary, the use of NIRS to evaluate cerebrovascular oxygenation and perfusion in neonates undergoing CHD repair is a promising area of research with the potential for real-time clinical implications.[9]

Patent ductus arteriosus

A persistent PDA can have clinical consequences in neonates. Although there is a recent trend for less aggressive treatment of PDA as many close spontaneously, a subgroup of preterm infants likely still benefits from closure. A PDA that has failed to close or where there are contraindications to medical therapy and is still considered to be clinically and hemodynamically significant commonly still progresses to surgical ligation.[29, 30] A hemodynamically significant PDA may exacerbate the common complications of prematurity (e.g., bronchopulmonary dysplasia, NEC, retinopathy of prematurity, and IVH) based on the degree of increased pulmonary blood flow and systemic hypoperfusion with diastolic runoff, cardiac dysfunction, and associated perinatal characteristics that affect the shunt.[31] However, significant uncertainty surrounding surgical closure of the PDA and its association to long-term improvement in clinical outcomes still exists.[32–39] Observational studies have demonstrated an association with an increased risk of bronchopulmonary dysplasia, retinopathy of prematurity, and neurodevelopmental impairment following PDA ligation, but this increased morbidity may be due to bias confounded by specific indication for ligation.[30]

Even as rates of PDA ligation decline worldwide, it is still recognized that definite closure with surgical ligation places infants at risk related to thoracic dissection, lung retraction, anesthesia, and postligation cardiac syndrome (PLCS) in extremely preterm infants.[32, 40–43] Infants undergoing surgical ligation of the PDA are exposed to low $rStO_2$ values for a prolonged period of time and are at risk of cerebral perturbations.[44] However, it remains unclear if long-term outcomes result from effects of anesthesia, surgery, length of ductal steal, or changes in cerebrovascular hemodynamics.[45] There is a growing body of literature that has explored the utilization of NIRS monitoring in infants undergoing surgical PDA ligation to provide a comprehensive understanding of the unique physiological considerations in extremely low birth weight infants.[44–50]

Pretreatment cerebral oxygenation. Infants with a hemodynamically significant PDA have evidence of lower presurgical baseline cerebral $rStO_2$ and higher cerebral FTOE compared to infants with a nonhemodynamically significant PDA or infants without a PDA at all.[44–50] Lemmers et al. observed that longer reduction of cerebral $rStO_2$ in preterm infants throughout the neonatal period was associated with decreased brain volume at term-equivalent age, and was most profound in infants undergoing surgical closure of the PDA.[45] Evidence has also shown that some infants undergoing PDA ligation developed cerebral $rStO_2$ values <40% during surgery, but before clipping, indicating a risk of hypoxic brain damage when scheduled for surgery.[44, 51] While presurgical persistent hypoxia may play a key role in the neurodevelopmental

outcome, it is likely that individualized assessment and targeted management is needed based on gestational age, birth weight, and clinical status.[52] Cohen et al. demonstrated that small-for-gestational-age neonates with a hemodynamically significant PDA prior to the medical or surgical intervention had a fall in $rStO_2$ over the first 3 days of life (69–61%, $P < 0.001$) with a rise in FTOE (0.26–0.34, $p < 0.001$) compared to appropriate-for-gestational-age preterm infants.[52] While this is only one study designed to measure the association between small-for-gestational-age neonates, the PDA and cerebral oxygenation, the true impact of fetal growth restriction, PDA, and the neurodevelopmental outcome is challenging to interpret due to the heterogeneity of literature.[53]

Changes of cerebral oxygenation during and after surgical closure of PDA. There is a paucity of robust data evaluating perioperative NIRS in preterm infants undergoing PDA closure. We summarized seven available small observational studies with both pre- and postoperative NIRS monitoring in Table 2 (weighted means, weighted for sample size).[44, 46–48, 50, 54, 55] Collectively, the data indicated a decline from preop cerebral oxygenation values to values obtained minutes after clipping, while there was an observed increase from preoperative cerebral oxygenation values to values determined beyond 12–24 h after surgery (Table 2). It appears that infants requiring surgical ligation could be at higher risk for significant changes in cerebral oxygenation; however, the data need to be interpreted within its main limitations of small sample size.

Cerebral autoregulation and oxygen metabolism with PDA physiology. The recognition that cerebral $rStO_2$ at 24 h after surgical closure is higher than pretreatment baseline and reached levels reported for preterm infants with nonhemodynamically significant PDA or no-PDA may partially be explained by fluctuations in cerebral perfusion and oxygen metabolism.[49] Kooi et al. reported impaired cerebral autoregulation during and following PDA ligation in nine preterm infants.[55] Interestingly, Kooi et al. also found a more pronounced alteration in cerebral autoregulation in the four infants undergoing posterolateral thoracotomy vs. sternotomy ($n = 5$). Impaired cerebral autoregulation has also been implicated for worse neurodevelopmental outcomes after surgical PDA closure compared to medical treatment.[32, 33, 49] Despite the promising mechanistic links between cerebral autoregulation, cerebral oxygenation, and a hemodynamically significant PDA preoperatively, the assessment of autoregulation remains primarily a research tool as it requires independent simultaneous measurement of both CBF and arterial blood pressure (or proxies of each).

NIRS monitoring can also be combined with measurements of CBF to compute an index of cerebral oxygen metabolism, known as the cerebral metabolic rate of oxygen ($CMRO_2$). Only one study has evaluated $CMRO_2$ in preterm infants undergoing treatment for a PDA, of which 2/8 progressed to ligation.[56] However, CBF was measured with a bolus-tracking NIRS technique using the light-absorbing dye indocyanine green as an intravascular contrast agent, an approach that remains in the research arena with little longitudinal clinical applicability. Other groups are exploring innovative noninvasive bedside combination of frequency-domain NIRS (intensity-modulated illumination and phase-resolved detection) and diffuse correlation spectroscopy (FDNIRS-DCS) to compute $CMRO_2$ from measured cerebral oxygen saturation and CBF during perioperative closure of the PDA.[57] Despite the data supporting the feasibility of NIRS monitoring, wide implementation to provide estimates of autoregulation and oxygen metabolism in real-time can only be achieved with larger sample size studies and a complete understanding of the relevant clinical short- and long-term outcomes. However, even without larger prospective studies, NIRS-derived cerebral oxygenation, autoregulation, and oxygen metabolism are important complementary monitoring parameters in the comprehensive hemodynamic assessment of neonates during this perioperative setting.

NIRS monitoring and PLCS. Postoperatively, some preterm infants may develop significant cardiopulmonary compromise, described as PLCS.[58–64] This represents a form of LCOS that occurs secondary to alterations in loading condition on the left side of the heart (decreased preload and increased afterload) and the upstream impact on the pulmonary vasculature following the abrupt closure of the PDA.[65] PLCS is associated with increased mortality[61] and morbidity.[66] Although the clinical phenotype of PLCS presents within 6–12 h after surgical ligation related to the rise in afterload, cardiac output can decrease immediately after ductal ligation[67] and potentially increase the risk of long-term neurodevelopmental impairment in survivors.[35] Definitive closure should increase CBF due to resolution of ductal steal, but the initial short-term decrease in cerebral $rStO_2$ observed after closure may be harmful to those infants with low presurgical baseline cerebral $rStO_2$.[44, 51] Prior to recognition, PLCS had been present in up to 45% of premature neonates with risk factors including younger gestational age at birth, smaller birth weight, earlier age at ligation, larger PDA size, and degree of preoperative cardiorespiratory support.[29] Continuous perioperative monitoring may aid in optimizing different anesthesia techniques (e.g., ventilation and sedation) that can prevent PLCS and reduce the risk of abnormal cerebrovascular hemodynamics, especially in infants with identified presurgical risk factors (altered contractility, diastolic dysfunction, and low afterload).[64, 68–70] Similar to the approach with the repair of CHD, monitoring renal, cerebral $rStO_2$, and somatic-cerebral difference might provide further diagnostic information.[71]

NIRS and percutaneous transcatheter closure. In 2019, the US Food and Drug Administration approved the Amplatzer Piccolo™ Occluder (Abbott Laboratories, Chicago, IL) for catheter-based closure for PDA in extremely low birth weight infants.[72] Transcatheter closure of the PDA represents a minimally invasive, nonsurgical alternative to achieve ductal closure as these devices are delivered with the use of venous access alone and are deployed under transthoracic echocardiogram and fluoroscopic guidance, removing the need for arterial instrumentation.[29] Transcatheter PDA closure appears to circumvent many of the respiratory, thermoregulation, and anesthesia risks of surgical ligation. While percutaneous ductal closure techniques have recently become more common, they are certainly not devoid of risk with reported procedural complications including device embolization and migration.[72, 73] The occlusion device can also cause aortic arch or left pulmonary artery obstruction if not appropriately seated within the PDA.[72, 73] The risk of LCOS is still present as recent data reports diminished left ventricle systolic function and oxygen failure in some smaller infants following transcatheter device closure, although the overall incidence appears decreased compared to ligation.[65] Future research is needed to understand the effects on cerebral oxygenation during the procedure.[74–79]

NONCARDIAC COMPLEX NEONATAL SURGERIES

Noncardiac major congenital anomalies requiring surgery in the neonatal period carry an increased risk of abnormal neurodevelopment, even after the exclusion of syndromes and chromosomal disorders.[1] Prospective evaluation of the incidence and pattern of brain injury after noncardiac complex neonatal surgery found mild to moderate brain lesions in 52%, and nonparenchymal abnormalities in 35% of patients.[2] The type of lesions observed (e.g., punctate white matter cluster or linear lesions and hemorrhagic punctate white matter lesions) were consistent with

hypoxic–ischemic episodes or altered blood flow patterns.[2] Perioperative NIRS may potentially aid in characterizing factors associated with the etiology and timing of brain injury in noncardiac neonatal complex surgery. We present the current state of the neonatal literature with respect to neurosurgical interventions and gastrointestinal surgeries with a focus on posthemorrhagic ventricular dilatation, NEC, and ECMO.

Neurosurgical interventions

Neurosurgical interventions can be essential in the treatment of disturbed cerebrospinal fluid (CSF) dynamics, myelomeningocele, and some progressive intracranial hemorrhage in preterm and term neonates. Data on NIRS monitoring in neonates undergoing neurosurgical interventions are limited with no published data on NIRS monitoring of myelomeningocele patients during defect closure or shunt surgery. However, there is an evolving body of evidence on NIRS monitoring of cerebral hemodynamics and oxygenation during or after CSF drainage in posthemorrhagic ventricular dilatation.[80–83] It is recognized that IVH is a major risk factor for long-term neurodevelopmental morbidity in preterm infants. Through several inflammatory and fibrotic processes, severe IVH can lead to obstruction of CSF drainage with increased intracranial pressure and dilatation of the ventricular system, commonly referred to as posthemorrhagic ventricular dilatation.[57] Ultimately, this process can impinge on the surrounding brain tissue and result in white matter injury and neurologic decline. As such, removal of CSF fluid with an understanding of the impact of cerebral oxygenation may provide essential intervention to mitigate long-term morbidity.[84]

Posthemorrhagic ventricular dilatation is associated with decreased $rStO_2$ and increased FTOE, suggesting a decrease in cerebral perfusion.[85] Norooz et al. measured cerebral $rStO_2$ values and calculated FTOE before and after decompression of posthemorrhagic ventricular dilatation in eight preterm infants and observed that cerebral $rStO_2$ was compromised before decompression and increased after intervention (42.6% (12.9) to 55% (12.2), $p = 0.0065$).[80] Cerebral FTOE decreased after decompression (0.51 (0.05) to 0.39 (0.12), $p = 0.015$). With an expected decrease in CSF volume and drop in intracranial pressure following an intervention, these authors suggest that NIRS may provide a complementary tool to aid in determining the optimal time point for ventricular decompression with recognition of low values of cerebral $rStO_2$ and increased values of cerebral FTOE.[80] Bembich et al. monitored 28 ventricular reservoir taps in four newborns to assess how much CSF volume removal is needed to improve cerebral hemodynamics and oxygenation.[81] Changes in the concentration of oxyhemoglobin and total hemoglobin, considered as estimates of CBF and volume, respectively, and cerebral $rStO_2$ were measured using NIRS. Cerebral $rStO_2$ values remained unchanged, but there was a significant improvement in cerebral hemodynamics with an increase in CBF and volume observed at 50% of the traditionally targeted 10 mL/kg CSF volume removal ($p < 0.001$). Variations in CBF and oxygenation were positively correlated with CSF removal ($r = 0.57$; $p = 0.002$). van Alfen-van der Velden et al. included seven term and preterm neonates in a study to evaluate the consecutive changes in cerebral hemodynamics and oxygenation following repetitive CSF removal in the first week after subcutaneous ventricular catheter reservoir placement.[83] The volume of repetitive CSF drainage was 7.6 ± 2.4 mL/kg with significant improvement of cerebral hemodynamics and oxygenation with the most pronounced effect observed following the initial removal of fluid.

The rise in cerebral oxygenation and decrease in oxygen extraction following CSF removal can be interpreted as increased CBF.[80–83] These changes were demonstrated with commercially available NIRS systems that monitor cerebral oxygenation by measuring light absorption at a few discrete wavelengths, referred to as continuous wave NIRS. McLachlan et al. combined hyperspectral NIRS, a technique that employs a broadband light source and a spectrometer to capture the entire attenuation spectrum, and the intravascular contrast agent, indocyanine green, to measure CBF, cerebral oxygenation, and cerebral oxygen metabolism in nine posthemorrhagic ventricular dilatation patients receiving a ventricular tap.[86] There was a significant increase in CBF (mL/100 g/min) following intervention (14.6% (4.2) to 16.9% (6.6), $p = 0.006$), but no changes in $CMRO_2$ (1.00 (0.08) to 1.04 (0.10), $p = 0.33$), $rStO_2$ (58.9% (2.7) to 61.0% (2.8), $p = 0.35$), or FTOE (0.36 (0.003) to 0.34 (0.03), $p = 0.078$). In comparison to controls, $rStO_2$ prior to intervention was lower and FTOE was higher (58.9% (2.7) vs. 70.5% (2.4), $p = 0.004$ and 0.36 (0.03) vs. 0.25 (0.02), $p = 0.007$, respectively). Following the ventricular tap, all values of CBF, $CMRO_2$, $rStO_2$, and FTOE approached control levels. Similarly, Rajaram et al. used FDNIRS-DCS to show an increase in CBF, but no changes in $rStO_2$, or an oxidative metabolic state across multiple ventricular taps in four patients. Soul et al. also demonstrated a stable NIRS-derived oxidation state of cytochrome *c* oxidase in 23 infants following removal of CSF.[82] The uniform lack of a metabolic response across these studies[82, 86] following removal of CSF might be explained by an increase in cerebral perfusion, suggesting that reduced CBF prior to the intervention was not sufficient to impede oxygen delivery. CBF and $CMRO_2$ may have better sensitivity than $rStO_2$ in detecting posthemorrhagic ventricular dilatation-related effects on infant brain metabolism and development.[57] The current evidence may reflect a compensatory increase in oxygen extraction with reduced oxygen delivery in posthemorrhagic ventricular dilatation patients that can be mitigated with intervention. However, some might argue that it is not plausible to have a stable $CMRO_2$ with increase CBF while oxygen extraction remains the same. The observed differences may potentially be due to measurement imprecision, bias, or sampling of both the arterial and venous circulation. With the recognition that the NIRS technologies used throughout these studies vary widely, future investigation is now needed to standardize and understand the true impact of noninvasive approaches with FDNIRS-DCS-derived CBF, $CMRO_2$, $rStO_2$, and FTOE to guide therapeutic interventions.

The clinical significance of NIRS may lie in its ability to provide insight on the timing of intervention. However, the management of posthemorrhagic ventricular dilatation and hydrocephalus is further complicated with regards to the frequency and CSF volume to be drained to decrease intracranial pressure. Traditionally, the CSF volume removed is ~10 mL/kg,[81], but the decision concerning when to intervene is based on clinical signs and cranial ultrasound scans. Preterm neonates are exquisitely sensitive to changes in CBF (both hypoperfusion and hyperperfusion) with potential cerebral autoregulation impairment with posthemorrhagic hydrocephalus.[87–89] As such, monitoring of cerebral oxygenation and cerebral autoregulation could help to determine the optimal timing, frequency, and CSF volume needed to be drained and ultimately prevent significant neurologic sequelae. It might be possible that higher intracranial pressure values could be tolerated with intact autoregulation. Coupled with clinical observation, disturbances of cerebral oxygenation and cerebral autoregulation could then indicate that CSF drainage is indicated, but larger randomized controlled trials are warranted.[90, 91]

Gastrointestinal surgeries

Neonatal gastrointestinal surgeries aim to address congenital malformations (e.g., esophageal atresia, omphalocele, gastroschisis, congenital diaphragmatic hernia) or acquired perturbations (e.g., spontaneous intestinal perforation or NEC).[10] Studies have explored perioperative use of cerebral and splanchnic NIRS in neonatal gastrointestinal surgeries. There is a lack of known risk factors influencing neurodevelopment outcomes with gastrointestinal neonatal surgeries, but the highest rate of impairment and

the greatest differences with cerebral NIRS monitoring have been observed among infants with a congenital diaphragmatic hernia and the need for ECMO.[1] Abdominal wall defects or esophageal atresia convey a more heterogeneous impact on neurodevelopment. Close monitoring of the intestinal perfusion, circulatory, and ventilatory status is needed in each case to accurately characterize the hemodynamics and potentially adjust the anesthetic and surgical approaches. NIRS may offer a novel modality, as one component of comprehensive hemodynamic a monitoring system, to identify both altered splanchnic and cerebral perfusion in gastrointestinal surgeries, regardless of the underlying disease.

Recent studies have explored the role of cerebral NIRS in the repair of esophageal atresia,[92–94] congenital diaphragmatic hernia repair[93–95] the placement of G-tube,[96] closure of gastroschisis,[97] and other digestive surgeries in neonates,[10, 98] but the increased recognition of the lack of reliable tools to characterize NEC has examined the potential for NIRS as a predictive and diagnostic tool for surgical NEC.[99–106] Utilizing prospectively acquired NIRS data in preterm infants undergoing surgical intervention for NEC, Kuik et al. recently showed that preoperative intestinal $rStO_2$ was higher in survivors than nonsurvivors.[106] They also determined that all infants with an intestinal $rStO_2$ >53% survived and <35% died, suggesting that intestinal $rStO_2$ may provide added value to current conventional clinical and biochemical assessments in estimating survival of preterm infants after surgical NEC intervention.[106]

Several studies have reported NIRS data with relation to NEC development following packed RBC (pRBC) transfusion.[107–109] In 2018, Marin and Moore observed severe and ongoing deterioration in splanchnic FTOE following pRBC transfusion in a preterm infant.[108] Interestingly, as this neonate developed complicated NEC with intestinal perforation, no clinical evidence of an abdominal event was observed at the bedside, resulting in an implication that changes in NIRS parameters may precede clinically evident NEC. In another case report, Baserga et al. described splanchnic NIRS monitoring in a premature neonate who developed Bell's stage 2 NEC within 24 h of a pRBC transfusion.[109] Although splanchnic FTOE was observed to rise during the transfusion, a substantial and persistent drop in splanchnic oxygenation was present prior to the clinical onset of NEC symptomatology. Currently, the observational nature of these reports precludes definitive assessment of underlying physiologic mechanisms regarding a possible connection between transfusion and NEC. There is an ongoing secondary study from the Transfusion of Prematures Trial[110] aimed at determining whether abnormal cerebral NIRS measures are a better predictor of neurodevelopmental impairment than hemoglobin alone and whether abnormal splanchnic NIRS measures are associated with the development of NEC within the 48 h following a transfusion. However, until the concerns with uniform optical properties with NIRS monitoring are addressed, which accounts for and adjusts to the tissue heterogeneity of the gastrointestinal tract, the clinical application of splanchnic NIRS in the assessment of NEC or transfusion-related NEC remain speculative.[111] Furthermore, the limited nature of the data and paucity of robust relevant studies regarding pRBC transfusion and development of NEC must be considered to avoid misinterpretation without a strong association.

Other studies have evaluated the utility of cerebral NIRS monitoring in addition to splanchnic monitoring as a predictive tool in the evaluation and management of suspected NEC.[103, 106, 112–114] In an observational cohort study, Kuik et al. utilized the relationship between NIRS-based cerebral FTOE and arterial blood pressure measurement to estimate cerebrovascular autoregulatory capacity among preterm neonates undergoing surgery for NEC and spontaneous intestinal perforation. More than half of the study participants demonstrated impaired cerebral autoregulation during their operative course, thus raising the question of whether NIRS could be used to improve perioperative management among this fragile population.[112] In another observational study, Schat et al. compared cerebral and splanchnic FTOE among preterm neonates who developed NEC vs. a matched cohort who never developed NEC. Neonates with cerebral oxygenation <70% within the first 48 postnatal hours demonstrated a higher likelihood of NEC development. Further, splanchnic FTOE was notably higher in the days preceding NEC diagnosis compared to non-NEC neonates who demonstrated a more consistent, non-rising splanchnic oxygen extraction.[113] In a separate study, lower cerebral $rStO_2$ was observed during the first week of age in preterm neonates who developed NEC compared to those who never developed NEC following adjustment for multiple confounders.[114] van der Heide et al. showed that lower cerebral oxygenation, lower splanchnic variability, and a higher splanchnic–cerebral oxygenation ratio (SCOR) values correlated with NEC diagnosis.[103] However, in a prospective blinded study, cerebral and splanchnic NIRS, in addition to SCOR determination, all demonstrated no differences between preterm neonates with NEC compared to neonates without NEC who had demonstrated acute gastrointestinal symptoms concerning NEC.[104] While both cerebral and splanchnic NIRS monitoring show promise for aiding in the diagnosis and management of NEC, further rigorous studies are clearly required to delineate specific monitoring strategies and associated clinical practices.

Extracorporeal membrane oxygenation

ECMO is a lifesaving support, currently used in patients suffering from severe but potentially reversible cardiopulmonary failure refractory to conventional therapy. Despite significant advances in neonatal intensive care (e.g., surfactant replacement therapy, high-frequency ventilation, and inhaled nitric oxide) reducing the need for ECMO, it is still required in selected patient[115] and its invasive nature can still expose patients to potentially severe clinical complications, of which neurological injuries can have the most impact on short- and long-term morbidity and mortality.[116] A retrospective analysis of neonatal ECMO use showed a 20% cumulative incidence of neurological complications, defined as brain death, cerebral ischemia, intracranial hemorrhage, and seizures.[117] Impaired neuromotor function, cognitive delay, and memory problems have also been reported in children who underwent neonatal ECMO.[118–121] Although neonates who require ECMO for respiratory failure have a reported survival rate of close to 90%, this population of children bears the highest incidence of neurological insults, often linked to both age and underlying disease.[122]

Perturbations of cerebral hemodynamics and cerebrovascular autoregulation play important roles in the occurrence of brain damage and subsequent adverse neurodevelopmental outcome in neonatal ECMO patients. Neonatal cerebral perfusion and cerebrovascular autoregulation in ECMO patients depend on the interplay between ECMO-related events and predisposing pre-ECMO features (e.g., gestational age, birth weight, hypoxia, acidosis, hypercapnia, myocardial impairment) linked to the severity of the underlying disease requiring extracorporeal support.[117, 123, 124] ECMO puts the brain at risk for damage due to several reasons. First, it confers profound changes in systemic hemodynamics and cerebral perfusion, starting from canulation itself. Carotid cannulation, in the case of veno-arterial (VA) ECMO, may induce the reduction in CBF, while jugular cannulation increases venous pressure in the superior vena cava, thus resulting in impaired cerebral venous drainage potentially with associated vascular brain damage of venous origin. Physiologic alterations (e.g., hypotension or hypertension) may also increase the risk for brain injury. Second, ECMO exposes neonates to potential embolic events from the circuit and hemorrhage due to the need for systemic heparinization. Third, both rapid changes in arterial partial pressures of oxygen/carbon dioxide and loss of arterial

pulsatility (often associated with ECMO in cases of full support) may contribute to cerebral vasomotor changes.

NIRS monitoring has been suggested as a preemptive neurocritical care tool to reduce adverse neurological outcomes in ECMO patients. In a recent survey on noninvasive neurocritical monitoring for neonates receiving ECMO, 50% ($n = 11$) of respondent Level IV neonatal intensive care units in the United States stated they routinely use cerebral NIRS monitoring for ECMO infants, and 8 of 11 for the duration of the ECMO run.[125] NIRS has been studied in different ECMO settings to evaluate, among others, the effects of vessel ligation and the ECMO starting phase. In one such study, 24 newborn infants were monitored by NIRS and a decrease in cerebral oxygenated hemoglobin was observed after carotid ligation, followed by significantly higher values 60 min after starting ECMO.[126] Similarly, van Heijst et al. found a bilateral reduction in cerebral oxygenation associated with carotid ligation, followed by an increase in CBF and oxygenation with ECMO initiation.[127] Ejike et al. studied a small pediatric population (9 newborns out of 11 pediatric patients) and observed a transient (17–45 min) 12–15% decrease in $rStO_2$ in the right frontal region during ligation of the right carotid artery, followed by a transient increase above baseline (results based on three patients), while no changes were observed during "trialing off" periods.[128] In six neonates undergoing VA ECMO, Papademetriou et al. demonstrated with multichannel NIRS a loss of cerebral autoregulation at low ECMO flows.[129] In addition, they observed differences between right and left cerebral hemispheres; right channels showed higher values of cross-correlation between mean arterial pressure and tissue oxygenated hemoglobin, suggesting that the right hemisphere was more susceptible to disruption of cerebral autoregulation. Data obtained from a piglet animal model also demonstrated an increase in cerebral blood volume after the canulation procedure (carotid and jugular ligation), which could presumably be attributed to cerebral venous congestion due to jugular ligation.[123]

Measurement of $rStO_2$ has proven to be a strong prognostic factor for both cerebral lesions and survival in 34 infants <3 months of age on ECMO with deceased and brain-injured infants showing lower values.[130] These findings have been supported by a study on 153 patients (1 day–20 years, 53.9% neonates) showing that the presence of any $rStO_2 \leq 50\%$ or any decline >20% from baseline was associated with unfavorable outcome (favorable outcome defined as survival with Pediatric Cerebral Performance Category (PCPC) ≤ 2 at hospital discharge or no decline from baseline PCPC).[122]

More recently, FDNIRS had been proposed to detect intracranial complications during ECMO by measuring regional light absorption and scattering in seven pediatric patients, of which two were newborns.[131] Cruz et al. also suggested the use of cerebral NIRS to predict the need for ECMO initiation in patients with congenital diaphragmatic hernia. These researchers identified that the difference between the right and left hemispheric $rStO_2$ was a reliable early and more robust predictor of ECMO use than current markers, with right hemispheric $rStO_2$ values decreased before canulation.[95] In summary, ECMO studies that have evaluated NIRS use in neonates suggest an evolving role for these measures to be used as outcome markers in ECMO-based research, but until further large-scale studies are conducted, caution still remains on its clinical impact.

CONCLUSIONS: NEXT STEPS AND FUTURE INITIATIVES

Perioperative neonatal NIRS applications to monitor central and peripheral $rStO_2$ with a goal of limiting postoperative neonatal complications in cardiac and noncardiac complex surgery are of increasing interest. Ultimately, it appears that NIRS may be used for several different noncardiac surgical procedures to provide clinical information concerning tissue oxygen delivery and utilization in neonates. We recognize that future NIRS-based investigations will be required to examine current diagnostic methods and their limitations. In addition, further study is needed to evaluate emerging noninvasive imaging techniques in association with NIRS to better define normal vs. abnormal physiologic function in the neonatal perioperative population.

While the NIRS monitoring technique demonstrates important clinical promise, several limitations and inconsistencies continue to hamper more widespread usage. Substantial variability in methods related to NIRS measurement include: (1) differences between equipment (design of devices, sensors, and proprietary data reporting algorithms); (2) individual user data capture and handling; and (3) postprocessing data interpretation. As such, $rStO_2$ and FTOE values are quite challenging to compare between NIRS devices from different manufacturers with numerous important differences reported.[5–7] Until an international neonatal task force is convened to standardize the approach to NIRS (e.g., approved devices, recommendations for data capture, and synchronized error/artifact correction),[7] widespread use for clinical neonatal perioperative monitoring will be challenging to implement in a consistent fashion. Currently, most investigators do not suggest relying on specific absolute $rStO_2$ thresholds to guide management, but would consider NIRS for perioperative trend monitoring only in conjunction with other vital parameters. Large prospective randomized control trials that assess feasibility, risk–benefit ratios, and correlations with clinical outcomes are required in a variety of neonatal surgical settings.

Contemporary science related to routine clinical assessment and care in each situation, ongoing challenges, knowledge gaps, and recommendations for research opportunities are presented in Table 1. These recommendations can serve to promote the implementation of standardized protocols that utilize NIRS monitoring as a complementary modality of hemodynamic assessment in neonates undergoing a surgical procedure. Multidisciplinary approaches that include teams of neonatologists, neurologists, cardiologists, pulmonologists, neuro-, cardiothoracic-, and general surgeons, physicists, and basic scientists are essential for the comprehensive clinical research needed to link NIRS measures in these different neonatal surgical procedures to outcomes; these data may provide answers regarding causality and lead to the development of prevention strategy for adverse outcomes

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ACKNOWLEDGEMENTS

Financial support of publication costs by the European Society for Paediatric Research (ESPR) is gratefully acknowledged.

AUTHOR CONTRIBUTIONS

All members of the European Special Interest Group "Near-InfraRed Spectroscopy" have substantially contributed to the conception and revision of the manuscript and approved the final version to be published.

COMPETING INTERESTS

The authors declare no competing interests.

PATIENT CONSENT

Patient consent was not required.

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