Near-infrared spectroscopy: What we know and what we need to know—A systematic review of the congenital heart disease literature

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Objectives: Neurologic dysfunction is a problem in patients with congenital heart disease. Near-infrared spectroscopy may provide a real-time window into cerebral oxygenation. Enthusiasm for near-infrared spectroscopy has increased hopes of reducing neurologic dysfunction. However, potential gains need to be evaluated relative to cost before routine implementation. Responding to data in ways that seem intuitively beneficial can be risky when the long-term impact is unknown. Thus, we performed a systematic review of the literature on near-infrared spectroscopy in congenital heart disease.

Methods: A literature search from 1950 to April 2007 for near-infrared spectroscopy in congenital heart disease was undertaken. We identified 54 manuscripts and 13 reviews.

Results: There were 47 case series, 4 randomized trials, and 3 retrospective studies. Two studies had postdischarge follow-up, one incorporating neurologic testing. Neither of these studies demonstrated a benefit. One retrospective study, which included near-infrared spectroscopy and other intraoperative measures of cerebral perfusion, demonstrated a decrease in neurologic dysfunction using this combination of monitors. Three small studies were able to correlate near-infrared spectroscopy with other clinical and radiologic findings.

Conclusions: Many centers, and even entire countries, have adopted near-infrared spectroscopy as standard of care. The available data suggest that multimodality monitoring, including near-infrared spectroscopy, may be a useful adjunct. The current literature on the use of near-infrared spectroscopy alone, however, does not demonstrate improvement in neurologic outcome. The data correlating near-infrared spectroscopy findings with indirect measures of neurologic outcome or mortality are limited. Although near-infrared spectroscopy has promise for measuring regional tissue oxygen saturation, the lack of data demonstrating improved outcomes limits the support for widespread implementation.

Supplemental material is available online.

Neurologic dysfunction is a significant problem in congenital heart disease (CHD). Historically, cardiac surgeons and cardiologists have had significant interest in acute clinical neurologic abnormalities such as stroke and seizure. With improved perioperative care, however, the prevalence of major acute neurologic abnormalities has decreased to 1% to 2% of open heart cases.¹ Of growing concern are late neurodevelopmental and behavioral problems associated with pediatric cardiac surgery.² These late neurologic impairments are compounded in children who require multiple

operations. With increasing overall survival, the understanding of the impact of long-term neurologic sequelae on quality of life is crucial. Significant efforts from physicians and industry have been directed toward developing improved monitoring techniques for early detection of neurologic injury in hopes of averting or ameliorating subsequent complications. Current technologies include transcranial Doppler, electroencephalograms, bispectral index, biomarkers, and jugular bulb oximetry. Physician enthusiasm has increased for the use of near-infrared spectroscopy (NIRS) in the perioperative period in hopes of reducing neurologic dysfunction.

NIRS is based on the differential absorption of varying wavelengths of light by hemoglobin as it associates with oxygen. It provides a regional measurement of oxygen content in a localized tissue bed. The device can be used for both cerebral and somatic regional measurements. The value reported represents the amount of oxygen present within the tissue, including arterioles, capillaries, and venules. The measurement is venous weighted (85% venous, 15% arterial). The purported value of cerebral NIRS is the ability to obtain noninvasive, real-time information on the cerebral oxygen content in the frontal cortex that reflects both oxygen delivery and consumption. This information may help guide interventions by the surgical team or intensive care physicians to maintain theoretically safe cerebral oxygenation levels.

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Abbreviations and Acronyms

CHD = congenital heart disease
 MRI = magnetic resonance imaging
 NIRS = near-infrared spectroscopy
 rScO₂ = regional cerebral oxygen saturation

NIRS technology has been described in the adult and pediatric cardiac literature in multiple clinical settings, including the intensive care unit and operating room. As with any new technology, the potential clinical gains (and limitations) need to be critically evaluated before integration into routine patient care. Each additional monitoring device comes with an additional cost and with increasing patient care complexity. In addition, responding to data in ways that seem intuitively beneficial can be risky when the long- or even intermediate-term impact on clinical outcomes is unknown. Within this context, we conducted a systematic review of the scientific literature to examine the available evidence for the use of NIRS in the care of patients with CHD.

METHODS

Eligibility Criteria

Inclusion criteria for the literature search were limited to human studies, English language, and pediatric cardiac patients; all such manuscripts using NIRS in any area of pediatric cardiology and pediatric cardiac surgery were included. Editorials, case reports, and duplicates were excluded. We reviewed narrative reviews of the use of NIRS in pediatric cardiac patients to avoid publication bias and to highlight the key difference between systematic and narrative reviews. The content of the narrative reviews was not included, as is customary, in the formal systematic review as it does not represent a primary scientific manuscript. All references were evaluated from the manuscripts to confirm inclusion of all pertinent studies.

Search Strategy

We searched the English language literature about the use of NIRS in the pediatric cardiac population from 1950 to April 2007 with MEDLINE, Pre-MEDLINE, EMBASE, and Cochrane databases. The MEDLINE search was performed combining the key word search: *near infrared spectroscopy*, *NIRS*, or *infrared spectroscopy*. This list was combined with a key-word search including the following: *pediatric cardiac surgery*, *CHD*, *pediatric*, *pediatric cardiology*, *intensive care*, *ICU*, *cardiopulmonary bypass*, *CPB*, *hypothermic circulatory arrest*, or *DHCA*. The results of the MEDLINE search are outlined in Figure 1. We identified a total of 224 manuscripts and we reviewed all abstracts. Manuscripts were excluded on adult patients, noncardiac patients, non-English language, editorials, single case reports, and duplicates. After these exclusions, a total of 48 manuscripts remained with an additional 8 manuscripts identified from the references of the narrative reviews. Further, we evaluated all articles classified as narrative review articles involving the patient population of interest along with their references to confirm an exhaustive review of the scientific literature.

Data Review and Analysis

We created a standardized data retrieval form. A single reviewer (J.C.H.) extracted data from the manuscripts and assessed clinical study site, study design, patient population, sample size, mode of monitoring, NIRS device, primary and secondary outcomes, intervention if any, and follow-up. We

subclassified manuscripts into general clinical sites for review and compilation (Figure 2). It was not possible to perform a meaningful meta-analysis with generation of a summary statistic owing to variation in end points, study design, monitoring device, and statistical analyses.

RESULTS

We identified 56 manuscripts that fit the eligibility criteria (Figure 1). We also identified and reviewed an additional 13 narrative review articles for comparative purposes. For simplicity of evaluation, we sorted the manuscripts by the clinical setting (Figure 2). Of the 13 review articles, 4 narrative reviews specifically focused on NIRS in the care of patients undergoing pediatric cardiac surgery.³⁻⁶ These review articles were not inclusive of all the potential clinical settings. The median number of manuscripts referenced within the review articles on NIRS and CHD patients was 8.5.³⁻¹⁵

The primary research manuscripts evaluated 6 different devices: INVOS (Somanetics, Troy, Mich), NIRO (Hamamatsu Photonics, Hamamatsu City, Japan), NIMS (NIMS Inc, Philadelphia, Pa), Radiometer (Copenhagen, Denmark), PSA-3N (Biomedical Science, Kanazawa, Japan), and In-spectra Tissue Spectrometer (Hutchinson Technology, Hutchinson, Minn). Owing to the natural progression of device technology, one can observe multiple models of the INVOS and NIRO devices evaluated in the literature. Various devices use different terminology to refer to cerebral oxygen content (Table 1).

Intraoperative Monitoring

A total of 38 manuscripts involved the use of NIRS in the intraoperative setting. The manuscripts were subdivided into 8 categories for summative purposes (Figure 3). Table E1 shows the author, year of publication, study design, monitoring device, patient population, number of patients, primary end point, and results. The manuscripts include 31 case series, 4 randomized trials, and 3 retrospective studies. The median sample size was 20 (range, 9–250). Two of the 38 manuscripts (in fact, the only 2 of the 56 overall manuscripts) had planned follow-up after hospital discharge; these follow-ups occurred at 3 months.^{16,17} One retrospective study assessed the role of an interventional algorithm on neurologic outcomes.¹⁸ They found that in patients with postoperative neurologic changes, more had noteworthy intraoperative cerebral perfusion changes (defined as a 50% decrease in cerebral blood flow by transcranial Doppler, excessive electroencephalographic slowing, or a decrease in regional cerebral oxygen saturation [rScO₂] by NIRS of > 20% for 3 minutes) that were not intervened on with a predetermined algorithm ($P = .003$).¹⁸ Three manuscripts evaluated the association of NIRS findings with direct clinical outcomes.¹⁹⁻²¹ One retrospective study ($n = 34$) demonstrated that patients who died after a single ventricle first-stage palliation had lower rScO₂ at the end of the operation ($P = .01$), but with no correlation to clinical neurologic abnormalities.²² Two case

FIGURE 1. Search strategy and study selection for inclusion. *Exclusion criteria: adult patients, non-English, noncardiac patients, editorials, case reports, and duplicates.

series correlated intraoperative NIRS measurements with postoperative magnetic resonance imaging (MRI) findings.^{19,21} One (n = 16)²¹ demonstrated that decreased rScO₂ during aortic crossclamping in patients was associated with abnormal postoperative MRIs ($P = .08$). The other (n = 22)¹⁹ found that prolonged low postoperative rScO₂ less than 45% for more than 180 minutes was associated with either new or worsening lesions on postoperative MRI ($P = .029$).

Intensive Care Unit Monitoring

Eleven manuscripts were identified that described the use of NIRS in the intensive care unit for patients with CHD. All of these manuscripts were case series, with a median sample size of 15 (range, 5–110). No studies contained neurologic follow-up assessments, nor did they correlate NIRS findings with clinical outcomes. Table E2 shows the author, year of publication, study design, monitoring device, patient popu-

lation, number of patients, primary end point, and results. Three studies focused on preoperative monitoring to define baseline values²³ and the response to hypoxia²⁴ and hypercarbia.²⁵ Seven studies focused on postoperative intensive care monitoring. These studies sought to correlate NIRS measurements with somatic NIRS measurements,^{26,27} alterations in ventilator management,^{28,29} sildenafil use,³⁰ and global measurements of systemic oxygenation.^{31,32} They identified correlations between rScO₂ and various traditional hemodynamic parameters (mean and systemic arterial pressure, arterial saturation, and mixed venous saturation). One study incorporated NIRS monitoring for single ventricle patients after stage 1 palliation on temporary ventricular assist devices. That study demonstrated a significant decrease in rScO₂ after the discontinuation of cardiopulmonary bypass. The decreased rScO₂ did not normalize for 48 hours despite normalization of other standard measurements such as lactate and mean arterial pressure.³³ The overarching findings in all of the studies were the presence of large interindividual variability and intraindividual temporal variability, which makes direct comparisons or determination of discrete safety measurements difficult.

Cardiac Catheterization Laboratory

Seven manuscripts were identified that described the use of NIRS for patients with CHD in the catheterization laboratory. All of these manuscripts were case series, with a median sample size of 29 (range, 11–98). None of these studies contained neurologic follow-up or correlated NIRS findings with clinical outcomes. Table E3 shows the author, year of publication, study design, monitoring device, patient

FIGURE 2. Classification of included manuscripts based on clinical application.

TABLE 1. NIRS devices and monitoring terminology

Device	Measurement	Abbreviation
INVOS	Regional oxygen saturation (cerebral or somatic)	rScO ₂ or rSO ₂
NIRO	Tissue oxygenation (oxyhemoglobin and deoxyhemoglobin), cellular oxygenation based on the oxidized state of cytochrome aa ₃ and the tissue oxygenation index	oxyHgb, deoxyHgb, total Hgb, Cytaa ₃ , TOI
NIMS	Regional cerebral oxygen saturation	ScO ₂
Radiometer	Tissue oxygenation (oxyhemoglobin and deoxyhemoglobin), cellular oxygenation based on the oxidized state of cytochrome aa ₃	HbO ₂ , Hb, cyt O ₂
PSA-3N	Regional cerebral hemoglobin oxygen saturation	SrO ₂
Inspectra tissue spectrometer	Tissue saturation	S _{TO2}

population, number of patients, primary end point, and results. As with the studies in the intensive care unit, many studies attempted to correlate NIRS findings with standard measurements of global oxygenation.³⁴⁻³⁸ One study correlated alterations in regional and global saturation with alterations in ventilation.³⁹ A second manuscript reported on the effect of balloon inflation during balloon dilation procedures in patients with and without intracardiac shunts. This study found that rScO₂ decreases with balloon inflation in patients with intracardiac shunts and that the recovery time is directly related to inflation time.⁴⁰ As with the studies in the intensive care unit, significant interindividual variability existed, making it difficult to compare patients.

CONCLUSIONS

Systematic reviews allow for a “pause” in the process of conducting research. They demonstrate, based on the available evidence, what we do know about a specific question. This information is then used to direct future research studies to clarify the areas of uncertainty. Systematic reviews follow a prospectively defined protocol to identify and appraise the relevant evidence. This is important in minimizing publication and information bias, which sets this methodology apart from traditional narrative reviews. Systematic reviews are limited by the quality of the original research being reviewed

and do not represent primary data. In addition, negative studies often do not reach publication, which can favor the treatment. Meta-analyses represent a type of systematic review that involves formal quantitative analyses of the summarized information. Meta-analyses require similar methodologies and outcomes measures for a summary statistic. With the wide variability in devices, small sample size, and variable end points, this was not possible with the available literature. Owing to the strength of minimizing bias, systematic reviews play an important role in clinical and health care policy decision-making.

Many centers, and even entire countries, have adopted NIRS as a standard of care (forum discussion at 2007 Congenital Heart Surgeons Society Meeting). Yet, no level I evidence-based medical research has been published to indicate that clinical decision-making based on NIRS data is beneficial to the patient. Although the continued desire to mitigate the neurologic complications associated with CHD and its surgical intervention is laudable, the role for NIRS in meeting that goal remains clouded by the lack of reliable scientific evidence.

This study provides a comprehensive review of the scientific literature on NIRS for patients with CHD. The majority of studies reporting on NIRS for this patient population are limited by their case series design, with no appropriate comparison groups, and with small sample sizes. In addition, the NIRS technology has changed significantly since its inception. The literature reflects these changes over time with 6 different NIRS technologies represented in articles we reviewed. Although all of the devices are based on the same theoretical premise of the monitoring of regional oxygenation, they employ various measurement indices, making it difficult to cull the data from multiple studies for comparison. The significant variability in NIRS measurements, temporally and between individual patients, precludes the establishment of absolute threshold values for tissue ischemia. Relative values and individual patient trends have been used rather than absolute values. However, there is only limited evidence to indicate that these correlate with clinical outcomes.^{18,41} Furthermore, the wide heterogeneity in anatomy and physiology in CHD patients results in

FIGURE 3. Classification of NIRS monitoring in the operating room.

varying baseline levels of oxygenation. In combination with the small sample sizes, the diverse patient populations studied cause extrapolation to the overall CHD population to be challenging, if not impossible.

The available data suggest that multimodality monitoring of cerebral perfusion, including NIRS, may be a useful adjunct to prevent neurologic injury.¹⁸ The current literature on the use of NIRS alone for CHD patients does not demonstrate a clinical improvement in short-term neurologic outcome. There are no prospective data evaluating NIRS findings with direct clinical outcomes. The data correlating NIRS findings with indirect measures of neurologic outcome, such as MRI or mortality, are also limited.^{19,21,22}

In assessing the potential role of NIRS monitoring in CHD, it is important to emphasize its unique qualities, including noninvasive, continuous, and real-time measurement of regional tissue oxygen saturation. However, caution must be exercised in extrapolating regional measurements to global findings. For example, alterations in regional oxygen saturation may reflect local changes and not necessarily indicate global hypoperfusion. Conversely, regional changes in oxygenation may be earlier, more sensitive indicators of impending multisystem organ injury. To date, no study has validated the correlation of NIRS measurements with other measurements of low cardiac output states. This is an important distinction when analyzing the literature in that reports of low regional cerebral oxygenation measurements do not necessarily indicate a low cardiac output state or global altered cerebral perfusion.

Future research needs to focus on how the addition of this regional oxygen saturation adds value to the clinical setting, rather than attempts to correlate NIRS with previously established global measurements of perfusion. Most important, before universal implementation of this technology, it is essential that rigorous clinical trials be performed to demonstrate improved clinical outcomes with the addition of NIRS monitoring.

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TABLE E1. NIRS monitoring in the operating room

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Anesthesia							
LeBlanc et al ¹⁶	2000	Randomized	NIRO	Elective ASD or VSD with (n = 11) or without (n = 13) propofol	24	Effect of propofol on the redox status of Cytaa ₃ and neurologic complications.	Propofol has similar effects on Cytaa ₃ as hypothermia; no gross neurologic complications.
Coarctation repair							
Berens et al ^{E42}	2006	Case series	INVOS	Aortic coarctation repair via left thoracotomy	26	Describe the changes in regional cerebral and somatic rSO ₂ with aortic XC.	The decrease in somatic rSO ₂ with XC is less in children than neonates and infants ($P < .01$), significant increase in cerebral rScO ₂ during XC in children > 1 year.
Azaki et al ^{E43}	2005	Case series	NIRO	Aortic coarctation repair via left thoracotomy	18	Determine whether aortic occlusion impairs left hemispheric cerebral oxygen balance.	Significant decrease in oxyHgb–deoxyHgb between the right and left ($P = .03$), significant decrease in oxyHgb–deoxyHgb with nitroprusside ($P < .001$).
Deep hypothermia with and without circulatory arrest (CA)							
Kussman et al ^{E44}	2005	Case series	INVOS	Infant biventricular repair (no arch reconstruction)	62	Evaluate the differences in bihemispheric measurement of rScO ₂ during hypothermic CPB.	No difference between right and left rScO ₂ measurements irrespective of CA
du Plessis et al ^{E45}	1995	Case series	NIRO	Infant biventricular repair with low flow or CA	63	Relationship between cerebral oxyHgb and Cytaa ₃	Median time to nadir of oxyHgb during CA was 25 minutes, increased total Hgb and oxyHgb above baseline with rewarming ($P < .001$) with delayed Cytaa ₃ recovery, dissociation between intravascular and mitochondrial oxygenation more pronounced in patients > 2 weeks
Kurth et al ⁴¹	1995	Case series	NIMS	Repair or palliation using CA	26	Variation in changes of intraop rScO ₂ between neonates, infants, children and are these changes associated with postop neurologic dysfunction	The half life of rScO ₂ during CA is longer for neonate > infants > children ($P < .001$), patients with neurologic complications had less of an increase in rScO ₂ on CPB and a significantly shorter cooling time pre-CA ($P < .05$), no significant difference in rScO ₂ between groups

TABLE E1. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Kurth et al ^{E46}	1992	Case series	NIMS	Neonates undergoing surgery with CA	17	Kinetics of oxyHgb in neonates during DHCA	OxyHgb increases during cooling ($P < .05$), decreases during CA in a curvilinear distribution until a plateau at 40 minutes ($P < .001$), and returns to baseline with rewarming
Greeley et al ^{E47}	1991	Case series	NIRO	Deep hypothermia with or without CA in neonates and children	15	The effect of CA on CMRO ₂ and oxygenation	OxyHgb and Cytaa ₃ decreased during CA, CMRO ₂ and Cytaa ₃ remained lower than baseline after CPB with CA but returned to normal in non-CA patients ($P < .01$).
Regional low flow perfusion (RLFP)							
Hofer et al ^{E48}	2005	Case series	INVOS	RLFP for Norwood procedure	10	Correlation of bilateral NIRS monitoring during RLFP with variable flow rates.	There was a significant decrease in bilateral rScO ₂ and jugular Svo ₂ with decreasing RLFP rates ($P < .001$). Wide interindividual variation in rScO ₂ .
Andropoulos et al ^{E49} (same patient sample)†	2004	Case series	INVOS	RLFP for Norwood procedure or aortic arch reconstruction	19	Correlation of bilateral NIRS monitoring during RLFP adjusted for CBFV with TCD.	During RLFP, correlation between hemispheres was poor and only partially returned to baseline after RLFP with the left side always being the lower value.
Hoffman et al ^{E50}	2004	Case series	INVOS	RLFP for Norwood procedure	9	Relative changes in cerebral and somatic oxygenation during RLFP adjusted for rScO ₂ and CBFV.	rScO ₂ was maintained during RLFP but decreased below baseline after CPB. There was no correlation between cerebral and somatic oxygenation at any time point.
Kilpack et al ^{E51} (same patient sample)*	2004	Case series	INVOS	RLFP for Norwood procedure or aortic arch reconstruction	34	Demonstrate maintenance of adequate rScO ₂ with RLFP when CPB flow adjusted for rScO ₂ and CBFV.	No difference in rScO ₂ on full flow CPB, RLFP, and resumption of full flow CPB. However, CPB flow was adjusted to maintain value within 10% of baseline.
Andropoulos et al ^{E52} (same patient sample)*	2003	Case series	INVOS	RLFP for Norwood procedure or aortic arch reconstruction	34	Describe the addition of CBFV monitoring by TCD to rScO ₂ as a guide to bypass flow during RLFP.	Poor correlation between MAP and required CPB flow. 14/34 had rScO ₂ > 95% during RLFP increasing the risk of hyperperfusion. No outcomes correlation for the addition of CBFV to rScO ₂ to guide CPB flow.

TABLE E1. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Andropoulos et al ^{E53} (same patient sample) [†]	2003	Case series	INVOS	RLFP for Norwood procedure or aortic arch reconstruction	20	Demonstrate the correlation between CBVI based on NIRS and CBFV by TCD.	Poor correlation between CBVI and CBFV. Right sided CBFV did not correlate with RLFP flow rate.
Pigula et al ^{E54}	2001	Case series	INVOS	RLFP for Norwood procedure or aortic arch reconstruction	15	Ability of RLFP to provide subdiaphragmatic somatic circulatory support as measured by somatic NIRS.	Abdominal aortic blood pressure, quadriceps blood volume, and quadriceps rSO ₂ were significantly greater during RLFP than DHCA ($P < .05$).
Pigula et al ^{E55}	2000	Case series	INVOS/NIRO	Neonatal aortic arch reconstruction with RLFP (n = 6) and neonatal cardiac repair with DHCA (n = 6)	12	Experiential report of using NIRS guided RLFP versus DHCA.	RLFP flow rate of 20 mL · kg ⁻¹ · min ⁻¹ maintained baseline values. rScO ₂ and CBVI decrease significantly during DHCA but are maintained during RLFP.
Perfusion techniques							
Han et al ^{E56}	2004	Randomized	INVOS	Repair of ASD or VSD with bloodless (n = 18) or blood (n = 18) prime	36	Compare the effect of blood versus bloodless CPB prime on rScO ₂ .	rScO ₂ decreases below baseline in both groups at the start of CPB and during rewarming ($P < .001$) with a greater reduction in the bloodless prime group ($P < .01$).
Sakamoto et al ^{E57}	2004	Randomized	NIRO	CPB in cyanotic patients using alpha-stat (n = 19) versus pH-stat (n = 21) strategy	40	Evaluate the effect of pH strategies on rScO ₂ and SPCC.	rScO ₂ was significantly lower ($P = .008$) and the deoxyHgb was significantly higher ($p < 0.0001$) with alpha-stat. SPCC was significantly lower with pH-stat ($P < .0001$).
Shaaban et al ^{E58}	2004	Case series	NIRO	Cold (25°C) (n = 9) versus warm (35°C) (n = 9) CPB for biventricular repair	18	Compare the effect of cold versus warm CPB in terms of extent of cerebral damage (measured by S100β) and oxyHgb.	S100β increased significantly in both groups. No correlation between S100β and NIRS measurements except lowest post-CPB Cytaa ₃ level ($P = .016$). TOI was significantly impaired during rewarming.
Wardle et al ^{E59}	1998	Case series	NIRO	Deep hypothermia (15°C) (n = 15) versus mild-moderate hypothermia (22°–28°C) (n = 15) CPB	30	Investigate the effect of hypothermia and CA on cerebral FOE.	FOE increases with the institution of CPB in cyanotic patients. FOE decreases during cooling and only increases during rewarming in the continuous flow group. No significant difference between groups at any time in Cytaa ₃ .

TABLE E1. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Chow et al ^{E60}	1997	Randomized crossover	NIRO	CPB using pulsatile and nonpulsatile flow	40	Examine the relationship between pump flow rate and cerebral hemodynamics during pulsatile and nonpulsatile CPB.	CBF decreased by 36% per L · m ² · min ⁻¹ decrease in pump flow rate regardless of pulsatility.
Kurth et al ^{E61}	1997	Randomized	NIMS	CPB: warm (n = 10), hypothermic (25°C) (n = 10), hypothermic/low flow (n = 9), and hypothermic/low Hct (n = 9)	38	Evaluate the effect of perfusate temperature, pump flow rate, and Hct on cerebral O ₂ extraction.	rScO ₂ increases during cooling (<i>P</i> < .001), rScO ₂ increased after CPB was discontinued in the low flow and low Hct group.
Intraoperative monitoring							
Fenton et al ²²	2007	Retrospective	INVOS	Single ventricle staged palliation (n = 34) and ductus-dependent complete repair (n = 12)	46	Determine whether rScO ₂ is related to the stage of single ventricle palliation.	rScO ₂ at the end of the operation was significantly lower in patients who died (<i>P</i> = .01), rScO ₂ decreases significantly after stage 1 palliation (<i>P</i> = .001) and increases after stage 2 palliation (<i>P</i> = .04). No correlation with neurologic complications.
Murayama et al ^{E62}	2006	Case series	NIRO	Repair of cyanotic (n = 10) and noncyanotic (n = 10) heart defects	20	Differences in rScO ₂ at the initiation of CPB for cyanotic and noncyanotic heart defects.	Cerebral oxyHgb, deoxyHgb, and total Hgb decrease and then plateau on CPB. DeoxyHgb and total Hgb decreased more markedly in the cyanotic patients (<i>P</i> < .01).
Fenton et al ²⁰	2005	Retrospective	INVOS	Repair of cyanotic and noncyanotic CHD	143	Determine CHD patient groups with abnormally low baseline rScO ₂ .	Preop rScO ₂ is lower in cyanotic and noncyanotic infants with left-to-right shunts (<i>P</i> < .01) but not in cyanotic infants without left-to-right shunts. Periop death was associated with a baseline rScO ₂ < 50%.
Hayashida et al ^{E63}	2004	Case series	PSA-3N	Noncyanotic CHD repaired with CPB	65	Measure the incidence of cerebral ischemia using bispectral index and NIRS in children having cardiac surgery.	Cerebral ischemia (defined as abrupt decrease in both rScO ₂ and bispectral index with acute hypotension) was more common and frequent in children < 4 years. rScO ₂ was more dependent on arterial pressure in children < 4 years. Cerebral ischemia frequency correlated negatively with Hct (<i>P</i> < .0001).

TABLE E1. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Morimoto et al ^{E64}	2003	Case series	NIRO	Repair of VSD	16	Examined changes in cerebral oxygenation using NIRS during VSD repair.	OxyHgb decreases on CPB with no change in deoxyHgb.
Daubeney et al ^{E65}	1998	Case series	INVOS	Biventricular repair	18	Identify periods of cerebral oxygen supply and demand mismatch using NIRS.	rScO ₂ decreased by > 15% in 10/18 patients before cannulation with cardiac manipulation. rScO ₂ increases with the institution of CPB and decays at 0.25%/min at < 20°C and 2%/min at > 20°C. rScO ₂ varied inversely with the rate of cooling ($P = .04$).
Austin et al ¹⁸	1997	Retrospective	INVOS	CHD repair with CPB	250	Examine the potential benefit of interventions based on intraop neurophysiologic monitoring (TCD, EEG, NIRS) in decreasing postop neurologic complications and length of hospital stay.	Of patients with neurologic changes, significantly more had noteworthy intraop changes that were not intervened on ($P = .003$) with significantly fewer of these patients discharged from the hospital within 1 week ($P < .05$).
Chow et al ^{E66}	1997	Case series	NIRO	Noncyanotic CHD repair with CPB	14	Explore the relation between arterial oxygen tension and CBF during CPB.	No relation between arterial oxygen tension and CBF. CBF is associated with CPB flow rate (decreases 4.2 fold per l/m ² /min).
Van Bel et al ^{E67}	1996	Case series	Radiometer	Neonatal and infant CHD repair with CPB	12	Investigate the changes in cerebral hemodynamics and oxygenation during DHCA.	CBV decreased significantly with cooling and increased significantly with rewarming ($P < .001$). CBV did not change with pump flow rate or MAP.
Fallon et al ^{E68}	1994	Case series	NIRO	Elective CHD repair with CPB	19	Measure the change in CBV associated with changing Paco ₂ (CBVR) under anesthesia and during hypothermic CPB.	CBVR is preserved under anesthesia and hypothermic CPB. The relationship between CBV and Paco ₂ is linear.

TABLE E1. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Skov and Greisen ^{E69}	1994	Case series	Radiometer	Biventricular cyanotic (n = 5) and noncyanotic (n = 9) CHD repair with CPB	14	Examine the changes in cerebral cytaa ₃ during induction of CPB.	In cyanotic patients, the total Hgb decreased rapidly and then reached a plateau, Cytaa ₃ decreased and oxyHgb index increased. There were no significant changes in the noncyanotic patients. The magnitude of the change in Cytaa ₃ was associated with the magnitude of change in total Hgb ($P < .0001$). Signal noise analysis raised concern about the validity of the results.
Fallon et al ^{E70}	1993	Case series	NIRO	Repair of CHD with CPB	13	Use of NIRS to monitor CBF, CBV, and CBVR.	CBVR significantly decreased during hypothermic (25°C) bypass.
Intraoperative combined with preoperative/postoperative monitoring							
McQuillen et al ²¹	2007	Case series	NIRO	Patients with CHD, preop/postop MRI and intraop NIRS	16	Define the risk factors for preop and postop brain injuries and association with functional cardiac anatomic groups (intraop NIRS was a secondary analysis).	TOI significantly decreased during aortic XC in patients with positive postop MRIs ($P = .008$).
Dent et al ¹⁹	2006	Case series	INVOS	Norwood procedure with RLFP, preop/postop MRI, preop/intraop/postop NIRS	22	Preop and postop MRI findings in neonates undergoing a Norwood procedure with RLFP.	Prolonged low postop rSco ₂ (<45% for >180 minutes) was associated with new or worsening lesions ($P = .029$) with a positive predictive value of 90% for positive MRI findings.
Toet et al ¹⁷	2005	Case series	INVOS	Transposition of the great arteries repaired with DHCA, preop/intraop/postop NIRS	20	Monitoring NIRS before, during, and after arterial switch operation to evaluate its relation to neurodevelopmental outcomes.	Recovery time for the EEG did not correlate with normalization of the rSco ₂ . Complete recovery of the rSco ₂ takes 6–72 hours postop. Preop decrease in rSco ₂ tended to correlate with decreased Bayley score but was not significant.

TABLE E1. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Monitoring technique							
Roberts et al ^{E71}	1998	Case series	NIRO	Repair of CHD with CPB	19	Describe a novel method to measure CBF using indocyanine green tracer with NIRS.	11% variation between measurements within individual patients, 73% of the variability was accounted for by pump flow and temperature.

ASD, Atrial septal defect; CA, circulatory arrest; CBF, cerebral blood flow; CBFV, cerebral blood flow velocity; CBV, cerebral blood volume; CBVI, cerebral blood volume index; CHD, congenital heart disease; CMRO₂, cerebral metabolism; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; EEG, electroencephalography; FOE, fractional oxygen extraction; Hct, hematocrit; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; oxyHgb, oxyhemoglobin; RLFP, regional low flow perfusion; rSo₂, regional oxygen saturation; SPCC, systemic–pulmonary collateral circulation; TCD, transcranial Doppler; TOI, tissue oxygenation index; VSD, ventricular septal defect; XC, crossclamp. *Evidence Based Medicine Levels of Evidence: *Level 1*, systematic review of randomized controlled trials (*RCTs*), individual *RCTs*; *level 2*, systematic review of cohort studies, individual cohort studies; *level 3*, individual case control studies; *level 4*, case series; *level 5*, expert opinion.

TABLE E2. NIRS monitoring in the intensive care unit

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Preoperative ICU monitoring							
Takami et al ²⁴	2005	Preop–postop	NIRO	CHD patients with increased pulmonary blood flow	8	Evaluate serial changes in oxygenation state in the head and body in patients with increased pulmonary blood flow.	With decreased Sao ₂ after the initiation of hypoxia, cerebral and brachial oxyHgb decreased with an increase in deoxyHgb
Ramamoorthy et al ²⁵	2002	Randomized crossover observational	NIM-prototype	Single ventricle neonates	15	Evaluate changes in rSco ₂ with inspired 17% Fio ₂ or 3% CO ₂	Significant increase in rSco ₂ and MAP with 3% CO ₂ , no change in rSco ₂ or MAP with 17% Fio ₂
Kurth et al ²³	2001	Case series	NIM-prototype	CHD and normal	110: 91 with CHD, 19 normal	Correlation of rSco ₂ and CEo ₂ between CHD patients and normals	rSco ₂ was significantly decreased in patients with PDA, TOF, HLHS, PA, SV with shunt, and BDG but was the same for VSD, CoA, and Fontan. CEo ₂ was significantly increased for PDA and HLHS. Sao ₂ was correlated with rSco ₂ but was not a good substitute ($R^2 = .4$)
Postoperative ICU monitoring							
McQuillen et al ²⁶	2007	Case series	INVOS	Postop CHD patients	70	Relationship between changes in rSco ₂ with changes in regional flank So ₂ and central Svo ₂ . Monitored for 24 hours.	Central Svo ₂ was correlated with rSco ₂ and flank rSo ₂ with wide limits of agreement precluding interchangeability. Changes in Paco ₂ and MAP were associated with changes in rSco ₂ but not flank rSo ₂ or Svo ₂ . Changes in Sao ₂ were associated with Svo ₂ but not rSco ₂ .
Mott et al ²⁸	2006	Case series	INVOS	Bidirectional Glenn (BDG)	10	Response of rSco ₂ to (1) hyperventilation with increased TV, (2) hyperventilation with increased RR, (3) hypoventilation with decreased RR. Monitoring for 4 hours.	(1) Increased pH, decreased Pco ₂ , and decreased rSco ₂ ; (2) same as 1; (3) no change in pH, increased Pco ₂ , and increased rSco ₂ . Hyperventilation should be avoided in patients with BDG due to potential decrease in rSco ₂ .

TABLE E2. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Nagdyman et al ³⁰	2006	Case series	NIRO	Elevated pulmonary vascular resistance after CPB	13	Examine alterations in cerebral oxygenation in children treated with increasing doses of sildenafil for elevated pulmonary vascular resistance. Monitored for 1 hour.	TOI increased significantly after the first two doses but quickly returned to baseline ($P = .01$), no change with the third dose. There was no correlation between cardiac index and TOI
Li et al ²⁷	2006	Case series	INVOS	Postop Norwood pateints	11	Determine if NIRS cerebral and splanchnic monitoring accurately reflects systemic oxygen delivery when compared with direct measurements. Monitored for 72 hours.	rScO ₂ correlates with SaO ₂ and PaO ₂ ($P < .0001$) with large interindividual variation, rScO ₂ correlates with Svo ₂ ($P < .0001$) with no interindividual variation. Overall, large interindividual variability and intraindividual temporal variability.
Bassan et al ²⁹	2005	Case series	NIRO	Postop CHD patients	43	Correlation of NIRS parameters (HbD = deoxyHgb–oxyHgb) with CBFV by TCD; identify pressure-passive cerebral perfusion by simultaneous measurements of HbD and MAP; and associate higher CO ₂ levels with pressure-passive cerebral perfusion. Measurements at 6 and 20 hours postop.	Significant relationship between change in CBFV and change in HbD ($P < .0001$), also with change in oxyHgb ($P < .001$). 13% of patients had disturbed cerebral pressure autoregulation at 6 hours that persisted at 18 hours, high end tidal CO ₂ was correlated with pressure passive rather than autoregulated cerebral perfusion ($P < .001$)
Tortoriello et al ³¹	2005	Case series	INVOS	Elective postop CHD patients	20	Compare rScO ₂ with Svo ₂ (oximetry) after pediatric cardiac surgery. Single measurement 6 hours postop.	rScO ₂ correlated with Svo ₂ ($P < .001$). There was low intrasubject variation with significant intersubject variation; therefore cannot predict absolute values but can follow trends.
Nagdyman et al ³²	2004	Case series	NIRO	Postop CHD patients	43	Determine the relationship between TOI as a value for regional rScO ₂ and global Svo ₂ (right atrial saturation via central line). Single measurement 2 to 3 hours postop.	TOI correlated with Svo ₂ ($P < .001$). Pao ₂ ($P = .031$), Sao ₂ ($P = .027$), SBP ($P = .035$), and MAP ($P = .042$). There was no correlation with Paco ₂ , heart rate, and hemoglobin.

TABLE E2. Continued

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Postoperative circulatory assist device monitoring							
Giacomuzzi et al ³³	2005	Case series	INVOS	HLHS with postop circulatory support	5	rScO ₂ on circulatory support after SV repair	rScO ₂ levels dropped significantly after separation from CPB and remained 20% below baseline for 24 hours and did not normalize until 48 hours despite stable Svo ₂ , MAP, and decreasing lactates.

BDG, Bidirectional Glenn; *CBFV*, cerebral blood flow velocity; *CEO₂*, cerebral O₂ extraction; *CHD*, congenital heart disease; *CoA*, coarctation of the aorta; *CPB*, cardiopulmonary bypass; *FIO₂*, inspired oxygen fraction; *ICU*, intensive care unit; *HLHS*, hypoplastic left heart syndrome; *MAP*, mean arterial pressure; *NIRS*, near-infrared spectroscopy; *PA*, pulmonary atresia; *PDA*, patent ductus arteriosus; *RR*, respiratory rate; *rScO₂*, regional cerebral oxygen saturation; *SBP*, systemic blood pressure; *SV*, single ventricle; *TCD*, transcranial Doppler; *TOF*, tetralogy of Fallot; *TOI*, tissue oxygenation index; *TV*, tidal volume; *VSD*, ventricular septal defect. *Evidence Based Medicine Levels of Evidence: *Level 1*, systematic review of randomized controlled trials (*RCTs*), individual *RCTs*; *level 2*, systematic review of cohort studies, individual cohort studies; *level 3*, individual case control studies; *level 4*, case series; *level 5*, expert opinion.

TABLE E3. NIRS monitoring in the catheterization laboratory

Author	Year	Study design*	Device	Patient population	Total number	Primary end point	Results
Bhutta et al ³⁴	2007	Case series	INVOS	OHT annual biopsy	29	Correlation of rScO ₂ with IVC, SVC, and PA Sao ₂ on RA and 100%	rScO ₂ correlates with SVC and PA Sao ₂ on RA and 100%
Kirshbom et al ³⁸	2007	Case series	INVOS	Elective cardiac catheterization in single ventricle patients	20	Determine the best non-invasive predictor of SVC Svo ₂ as a marker of adequacy of systemic oxygen delivery.	NIRS was a significant independent predictor of SVC Svo ₂ ($P = .000$).
Levy et al ³⁵	2005	Case series	Inspectra Tissue Spectrometer	Elective cardiac catheterization	98 (50% with intracardiac mixing)	Evaluate tissues saturation (NIRS-deltoid) as a measure of Svo ₂	No correlation between tissue saturation and Svo ₂
Nagdyman et al ³⁶	2005	Case series	NIRO	Elective cardiac catheterization	60	Correlation between tissue oxygenation index (TOI) with jugular Svo ₂ (Sjo ₂)	Sjo ₂ does correlates with TOI with poor sensitivity of spatially resolved spectroscopy
de Vries et al ⁴⁰	2000	Case series	INVOS	Balloon dilation	11 (I: 6 no intracardiac shunt, II: 5 with intracardiac shunt)	Changes in cerebral hemodynamics (TCD) and oxygen metabolism (NIRS) during balloon dilation	With balloon dilation, significant decrease in velocity in the MCA with no change in rScO ₂ group I, significant decrease in rScO ₂ with no change in velocity in the MCA group II. Longer inflation time correlated with longer time to recovery
Watzman et al ³⁹	2000	Case series	NIM-prototype	Elective cardiac catheterization	20	Correlation of Sao ₂ , rScO ₂ , an Sjo ₂ with normocapnia/Fio ₂ 21%, normocapnia/Fio ₂ 100%, hypocapnia/Fio ₂ 21%	rScO ₂ correlates with Sao ₂ and Sjo ₂ . The arterial to venous ratio for rScO ₂ is consistent within patients but varies significantly between patients
Daubeney et al ³⁷	1996	Case series	INVOS	Pediatric CHD patients in the cath lab (29) and during cardiac surgery (11)	40	Determine if rScO ₂ reflects jugular bulb venous saturations.	Correlation between rScO ₂ and jugular bulb Svo ₂ was 0.69 ($P < .0001$) with decreased reliability at extremes.

CHD, Congenital heart disease; Fio₂, inspired oxygen fraction; IVC, inferior vena cava; MCA, main cerebral artery; NIRS, near-infrared spectroscopy; OHT, orthotopic heart transplantation; PA, pulmonary atresia; RA, radial artery; rScO₂, regional cerebral oxygen saturation; Sjo₂, jugular Svo₂; SVC, superior vena cava; TCD, transcranial Doppler; TOI, tissue oxygenation index. *Evidence Based Medicine Levels of Evidence: Level 1, systematic review of randomized controlled trials (RCTs), individual RCTs; level 2, systematic review of cohort studies, individual cohort studies; level 3, individual case control studies; level 4, case series; level 5, expert opinion.