Cerebral and Splanchnic Tissue Oxygenation Are Significantly Affected in Premature infants with Ductal-Dependent Congenital Heart Disease

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Objective To determine whether premature infants with prostaglandin (PGE)-dependent congenital heart disease (CHD) have impaired cerebral and splanchnic oxygenation (rSO_2) using near infrared spectroscopy (NIRS).

Study design Cerebral and splanchnic rSO_2 were monitored using NIRS for 48 hours in premature infants <36 weeks gestational age with PGE-dependent CHD and control infants (no CHD or patent ductus arteriosus). Both groups were receiving gavage enteral feedings and were >14 days of life. Mixed effects model estimated the effect of CHD and feedings on splanchnic and cerebral NIRS and accounted for multiple measurements on the same participant at 3 different times around feedings (30 minutes before, during, and 30 minutes after feedings).

Results Twenty-four participants were enrolled in the study (10 with CHD and 14 controls). The final dataset included 897 measurements from 23 participants. The median gestational age and birthweight were comparable between case and control groups (34 vs 33 weeks gestational age; mean birthweight of 1811 g vs 1820 g, respectively). On average, cerebral NIRS measurements were 9.5 points higher in controls than cases (P = .003); and splanchnic NIRS measurements were 13.1 points higher in controls than cases (P = .001). The mean cerebral NIRS measurements at baseline, during feeding, and after feeding were 64.0 ± 10.4, 64.5 ± 9.9, and 64.2 ± 9.9 in cases, respectively; and 73.3 ± 6.9, 73.1 ± 6.8, 73.5 ± 6.9 in controls, respectively. The mean splanchnic NIRS measurements at baseline, during feeding, and after feeding were 34.4 ± 15.8, 37.2 ± 14.8, and 38.3 ± 16.1 in cases, respectively; and 50.7 ± 11.0, 51.6 ± 11.1, 50.6 ± 13.5 in controls, respectively.

Conclusions These results demonstrate significantly lower cerebral and splanchnic rSO_2 in premature infants with PGE-dependent CHD compared with control infants. These data raise concerns regarding how unrepaired cyanotic CHD can limit systemic oxygenated blood flow chronically, directly contributing to cerebral and gastrointestinal hypoperfusion and ischemia, ultimately increasing the risk for poor neurodevelopmental outcomes and necrotizing enterocolitis in these premature infants. *(J Pediatr 2024;14:200126)*.

Congenital heart disease (CHD) is a leading birth defect in the US, affecting approximately 40,000 neonates annually. Owing to advances in medical care, survival rates have increased significantly in the preterm population. However, premature infants with prostaglandin (PGE)-dependent CHD are at high risk for morbidities such as feeding intolerance and/or necrotizing enterocolitis (NEC), as well as at risk for poor neurodevelopmental outcomes.[1-6] These premature infants sometimes remain in the neonatal intensive care unit (NICU) awaiting adequate weight gain to undergo repair, leaving them with a mixing circulation and hypoxemia for the first several days or weeks of life, and sometimes longer.

The pathophysiology of NEC in CHD patients remains unknown, but is thought to be multifactorial with chronically lower bowel perfusion pressures owing to lower diastolic pressures along with lower systemic oxygenated blood flow. This scenario may lead to gastrointestinal ischemia, loss of intestinal integrity, and bacterial overgrowth, ultimately increasing the risk for NEC.[7-9] To date, no studies have evaluated mesenteric saturations in premature infants with ductal-dependent CHD on PGE who are receiving gavage enteral feedings, during the time when they are at high risk of developing NEC before cardiac repair.

Although advances in medical and surgical techniques have improved survival from CHD, those innovations have not produced dramatic improvements in neurodevelopmental outcomes in infants with PGE-dependent CHD.[5,10,11] Moreover, large multicenter studies have excluded surgical factors as independent predictors of developmental delays.[10,12] Therefore, other potential causes that may contribute to developmental delays need to be identified. One of the potential causes of impaired neuro-

CHD	Congenital heart disease
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NIRS	Near infrared spectroscopy
PDA	Patent ductus arteriosus
PGE	Prostaglandin
rSO_2	Oxygenation

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https://doi.org/10.1016/j.jpedcp.2024.200126

development that has not been examined extensively is chronic cerebral hypoxia owing to systemic hypoxemia associated with PGE-dependent CHD.[13,14]

Tissue saturation can be continuously and noninvasively assessed using near infrared spectroscopy (NIRS) to measure the balance between oxygen delivery and consumption. NIRS uses light in the near infrared region of the electromagnetic spectrum to enable estimation of tissue rSO_2. NIRS oximeters provide an absolute value of tissue rSO_2 expressed as ratio of oxygenated to total hemoglobin in the tissue underlying the monitoring sensor. Therefore, NIRS has the advantage of measuring oxygen hemoglobin saturation in the venous, capillary, and arterial beds.

NIRS can be used at the bedside easily and has been used in premature infants to evaluate changes in the perfusion and rSO_2 of body tissues, including the mesentery and brain.[15-17] NIRS regional oxygen saturations (rSO_2) reflect a balance of tissue oxygen supply and demand and have the potential to monitor rSO_2 in multiple organs, with cerebral, renal, and splanchnic rSO_2 being the most frequently monitored in neonates.[16,18-20]

We hypothesized that preterm infants with PGE-dependent CHD will demonstrate preoperative decreased regional cerebral and splanchnic rSO_2 as measured with NIRS at >14 days of life when compared with control infants.

Methods

This study was a prospective, observational study carried out at the Level IV Primary Children's Hospital NICU in Salt Lake City, Utah. The Institutional Review Boards of the University of Utah and Intermountain Healthcare reviewed and approved this proposal. Informed consent was obtained from each participant's parent or legal guardian before the placement of monitoring devices or data collection. Study personnel approached families of eligible infants and enrolled infants between January 1, 2016, and December 31, 2021.

Infants were eligible if they were born at <36 weeks gestational age, were >14 days old, and were receiving enteral feedings by gavage feeding tube. For the purpose of this study, we compared 2 groups of infants. (1) The case group included infants with PGE-dependent CHD. (2) the control group included infants without CHD. Patients in the control group had no clinical signs of patent ductus arteriosus (PDA) and/or had had an echocardiogram to rule it out if there was a clinical concern (murmur). Infants with multiple congenital anomalies, in an unstable clinical condition (having clinical sepsis or requiring vasopressors), or with history of NEC, gastroschisis, or other abdominal pathology were excluded from the study.

NIRS Measurements

Research nurses placed the neonatal NIRS probes according to INVOS OxyAlert protocols on intact skin over the right or left frontal area (cerebral rSO_2) and midline in the infra-umbilical area of the abdomen (splanchnic). Cerebral and splanchnic rSO_2 were monitored continuously and recorded every 5 seconds using NIRS for 48 hours in premature infants <36 weeks gestational age with PGE-dependent CHD and control infants (no CHD). Each neonate NIRS measurements were analyzed before, during, and after each of the 12-16 feedings during the 48 hours monitoring period (**Figure 1**). We monitored for 48 hours because it would capture 16 feeding episodes and generate enough data to compare the 2 groups. The Medtronic INVOS 5100C Regional Oximeter (Medtronic, PLC, Minneapolis, MN) was used. The technical specifications of this device have been previously published.[21]

The splanchnic-cerebral rSO_2 ratio was calculated (rSO_2 splanchnic/rSO_2 cerebral) for the before feeding, during feeding, and after feeding time frames using the mean rSO_2.

Feeding Protocol

Infants in the CHD arm received human breast milk feedings according to the NICU cardiac protocol. Gavage enteral feedings were administrated continuously over 60 minutes for ≤60 mL/kg/day, depending on clinical status. The remainder of the nutrition was given as total parenteral nutrition intravenously. Infants in the control arm received gavage feedings also per NICU protocol (continuous gavage infusion of ≤60 minutes). The reason behind choosing >14 days of life is that we wanted to ensure full feedings were established in both the CHD and cohort groups. The feeding protocol we use in CHD infants advances feedings much slower than regular feeding protocols.

Statistical Analyses

We used means, SDs, and percents to summarize participant characteristics. The Student *t* test was used to compare quantitative participant characteristic variables across groups. The χ^2 test and Fisher's exact test were used compare quantitative patient characteristic variables across groups. We used a mixed effects model to estimate the effect of CHD and feedings on splanchnic and cerebral NIRS, with a random intercept for participant to account for multiple measurements on the same participant at 3 different times around multiple feedings (30 minutes baseline, duration of each feeding, and 30 minutes after feeding time). Data management and statistical analysis were done in the R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Results

Twenty-four participants were enrolled in the study (10 with CHD and 14 controls). One control participant was excluded from the dataset owing to a malfunctioning NIRS device that resulted in aberrant readings. The final dataset included 897 measurements from 23 participants. **Table** shows the characteristics of the study participants. There were no statistically significant differences in the mean gestational age at birth, percent female, or 5-minute Apgar scores. There were 5 small for gestational age infants in the CHD

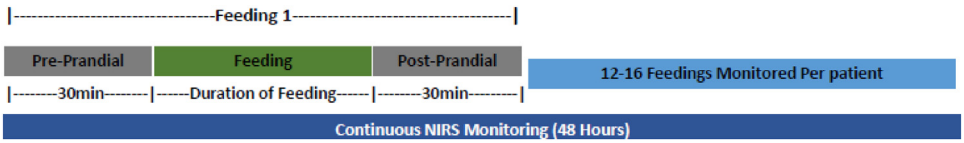

Figure 1. Data evaluated cerebral and splanchnic regional rSO_2 using NIRS measurements 30 minutes before each feeding, during of each feeding, and 30 minutes after feeding. Each infant was under continuous NIRS monitoring for 48 hours.

group and no small for gestational age infants among the controls. Table summarizes the CHD lesions affecting the 10 participants in the CHD group.

There was a statistically significant difference in splanchnic and cerebral NIRS values in cases compared with controls. On average, cerebral NIRS measurements were 9.3 points higher in controls than cases (P = .014). The mean cerebral NIRS measurements at baseline, during feeding, and after feeding were 64.0 ± 10.4, 64.5 ± 9.9, and 64.2 ± 9.9 in cases, respectively; and 73.3 ± 6.9, 73.1 ± 6.8, 73.5 ± 6.9 in controls, respectively. Splanchnic NIRS measurements were 13.1 points higher in controls than cases (P = .008) (Figure 2). The mean splanchnic NIRS measurements at baseline, during feeding, and after feeding were 34.4 ± 15.8, 37.2 ± 14.8, and 38.3 ± 16.1 in cases, respectively; and 50.7 ± 11.0, 51.6 ± 11.1, 50.6 ± 13.5 in controls, respectively. There was no difference in splanchnic-cerebral rSO_2 ratio values between cases and controls (P = .164). There was also no statistically significant difference in NIRS values (cerebral, splanchnic, and splanchnic-cerebral rSO_2 ratio) at baseline vs during feeding vs after feedings. There was no difference between groups in the first hematocrit obtained during NIRS monitoring (mean 39.6 ± 4.5 vs 44.7 ± 10.0; NIRS vs control; P = .130). There was also no difference between groups in the age (in days) when NIRS monitoring was started (mean, 21.7 ± 13.6 vs 20.1 ± 10.9; NIRS vs control; P = .754). The median age at time of first surgery for CHD was 38 days (range, 13-106 days).

Table. Characteristics of 23 study participants stratified by study group

Characteristics	CHD h (n = 10)	Control (n = 13)	*P* value
Gestational age at birth (weeks)	33.5 ± 2.5	31.5 ± 2.6	.083
Birthweight (g)	1811 ± 743	1820 ± 284	.968
Female sex	4 (40)	7 (54)	.510
Small for gestational age	5 (50)	0 (0)	.0024
CHD lesions			
Coarctation of the aorta (isolated)	5 (50)	NA	
Coarctation of the aorta (with additional lesions)*	3 (30)	NA	
Truncus arteriosus	1 (10)	NA	
DORV, aortic valve atresia, VSD	1 (10)	NA	

DORV, double outlet right ventricle; *NA*, not available; *VSD*, ventricular septal defect.
Values are mean ± standard deviation or number (%).
*Three participants had coarctation of the aorta in combination with other congenital heart lesions; one with coarctation and a double outlet right ventricle; one with coarctation and a ventricular septal defect; one with coarctation and pulmonary valve stenosis.

Discussion

Premature infants with PGE-dependent CHD are at significant risk for feeding intolerance[22,23] and/or NEC,[24-26] as well as at risk for poor neurodevelopmental outcomes.[11,27] The present study is the first prospective observational study to confirm an overall concomitant lower cerebral and splanchnic rSO_2 in premature infants with PGE-dependent CHD compared with premature control infants.

The pathophysiology of these morbidities are not well-understood and likely multifactorial. One leading hypothesis is that systemic perfusion is impaired by diastolic steal. Impaired perfusion, in turn, predisposes the infant to NEC,

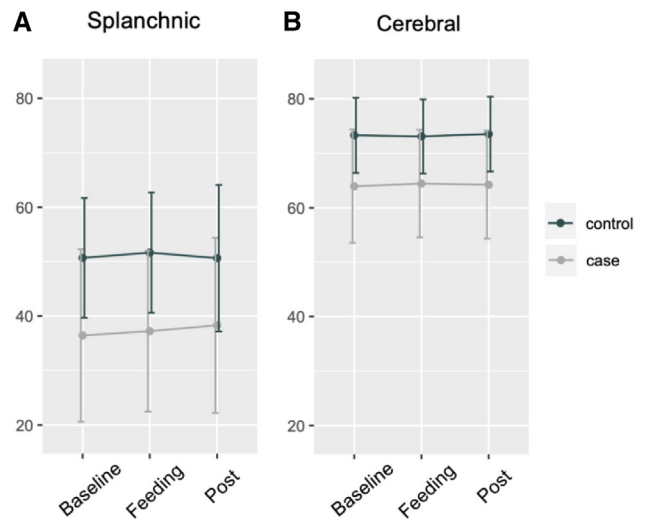

Figure 2. Cerebral and splanchnic regional rSO_2 measurements before, during and after feedings. Mean regional rSO_2 measurements 30 minutes before each feeding, during of each feeding, and 30 minutes after feeding. Mean values are separated by case (infants with PGE-dependent CHD; light gray) and control (dark gray). **A**, Splanchnic regional rSO_2 measurements. **B,** Cerebral and splanchnic regional rSO_2 measurements.

feeding intolerance, and/or poor brain development. Studies showing associations between changes in Doppler flow profiles in infants with CHD and the risk of NEC in term and preterm neonates support this hypothesis.[28,29]

NIRS is a noninvasive, real-time method to estimate tissue rSO_2. NIRS devices are designed to monitor cerebral, splanchnic, and renal rSO_2. NIRS has gained widespread popularity for neonatal applications including cerebral rSO_2 monitoring during cardiac surgery,[30] in cases of hypoxic ischemic encephalopathy,[31] in patients with posthemorrhagic ventricular dilation[32]; and splanchnic or renal monitoring in preterm infants with PDA,[18] hypovolemia, or cardiac dysfunction.[33] NIRS has also been used to evaluate rSO_2 of the brain, skeletal muscle, lung, kidney, and mesentery in premature infants with PDA. One study demonstrated lower baseline rSO_2 in infants with hemodynamically significant PDA.[34] The infants evaluated in this study had a median postnatal age of ≤10 days, and 70% of the infants were not fed at the time of NIRS monitoring. Few studies have used NIRS to evaluate mesenteric saturations in neonates with CHD. One study used NIRS to observe splanchnic rSO_2 throughout the introduction of feedings in infants with CHD post cardiac repair.

Infants with single ventricle repair were found to have significantly lower splanchnic rSO_2 than infants with a biventricular repair.[35] Another study showed that infants with cyanotic CHD has decreased cerebral oxygen delivery owing to arterial desaturation.[36]

Many infants with CHD are dependent on their ductus arteriosus to maintain systemic perfusion after birth and require PGE infusion for extended periods of time to maintain a PDA before surgical repair. This is demonstrated in our study population where the average time in the NICU before cardiac surgery was 38 days (range, 13-106 days). At our institution, these infants are worked up on feedings following a cardiac feeding protocol while awaiting cardiac repair. During their NICU stay, NIRS is used as standard of care to detect any abnormalities in the balance of cerebral and renal tissue oxygen delivery and consumption. However, splanchnic NIRS is not used typically.

However, NEC is the most common gastrointestinal disorder encountered in preterm and newborn infants with CHD and can result in significant morbidity and mortality. NEC prevention and treatment are significant challenges in daily patient care and constitute the focus of many ongoing bench and clinical research studies. Because NEC causes are multifactorial, prevention will require a multifaceted approach. As shown by previous reports, infants with PDA whether secondary to prematurity or CHD are at increased risk for NEC. One of the proposed pathophysiological explanations of NEC in the presence of a PDA is a result of blood flow being reversed from the mesenteric arteries back to the aorta, limiting systemic oxygenated blood flow and compromising diastolic gut perfusion. This leads to gastrointestinal hypoperfusion and ischemia increasing the risk of NEC.[2,34,37] This pathophysiological change has been shown in prior studies; premature infants with a hemodynamically significant PDA have decreased diastolic flow velocity of the mesenteric arteries when measured by Doppler ultrasound examination. They also have an attenuated intestinal blood flow response to feedings in the post prandial period compared with infants without PDA.[38-40] Therefore, accurate assessment of intestinal perfusion and rSO_2 in these at-risk infants may predict impending mucosal damage before the development of the full clinical picture of NEC.

Even though the pathophysiology leading to NEC and poor neurodevelopment in this population still need further clarification, the observations made in the present study can serve as hypothesis generating for larger trials as well as a starting place to support the development of feeding protocols in this at-risk population. Using continuous splanchnic NIRS as a noninvasive clinical tool to detect critically low splanchnic rSO_2 may help to determine which neonates are at risk for the development of NEC so that preventive changes can be made in their care before onset of the full NEC onset.

Because survival among children with CHD has improved in recent years, neurodevelopmental impairment has become a primordial focus in the assessment of clinical outcomes. Many premature infants with PGE-dependent CHD do not meet weight criteria to undergo repair right after birth and require prolonged hospitalization in the NICU, exposing them to chronic mixing circulation and hypoxemia. Because abnormal cerebral oxygen delivery is a key contributor in the neurodevelopmental pathophysiology of these infants, a better understanding of the cerebral O_2 status may assist in the development of strategies that can help to decrease the long-term effects of cerebral hypoxemia.

Based on these data, further studies are needed to establish whether NIRS can be used as a tool to better inform health care providers about significant alterations in splanchnic and cerebral rSO_2 in CHD patients at risk for NEC and poor neurodevelopmental outcomes.

A limitation of our study is that it was conducted at a high elevation in Utah, whereas prior studies were performed at locations near sea level. We are not certain of the effects of high altitude in the CHD premature population, but speculate that if altitude played a significant role our control group would have shown lower parameters at baseline than those published previously. A second limitation is that NIRS signal quality can be affected when measuring splanchnic rSO_2 compared with other body sites. This is often due to the changing nature of intestinal contents (stool, peristalsis and air) vs a solid organ such as the kidney.[33,37] This results in much larger SDs when compared with renal and cerebral NIRS measurements and represents a limited factor of the NIRS technology.

An important limitation of this small sample study was that most of the infants in the CHD cohort were not followed up in our neurodevelopmental follow-up clinic and neither were the control infants. Also, the CHD pathology most observed in this study was limited primarily to coarctation of the aorta (8 of 10 participants). Therefore, the results may not translate to other CHD types. We also found that more infants in the CHD arm were small for gestational age. The postoperative NIRS data were not available to

demonstrate whether cerebral and splanchnic rSO_2 normalized after surgery. Finally, although the sample size in the CHD cohort limits the significance of our findings, the inclusion of a healthy control group constitutes a strength.

In conclusion, this observational study demonstrated that preterm neonates with PGE dependent CHD had a significant decrease in both splanchnic and cerebral rSO_2 when compared with a matched gestational age control group. Although there remain many unanswered questions that need more research to help understand and interpret the NIRS data, these results raise concerns regarding how unrepaired cyanotic CHD can persistently limit systemic oxygenated blood flow directly contributing to cerebral and gastrointestinal hypoperfusion and ischemia, ultimately increasing the risk for poor neurodevelopmental outcomes and NEC in premature infants with (PGE)-dependent CHD. ■

CRediT authorship contribution statement

Anastasiya Mankouski: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation. **Timothy M. Bahr:** Writing – review & editing, Visualization, Software, Funding acquisition, Formal analysis. **Katherine L. Braski:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Kimberlee Weaver Lewis:** Supervision, Resources, Funding acquisition. **Mariana C. Baserga:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Submitted for publication May 6, 2024; last revision received Sep 6, 2024; accepted Sep 11, 2024.

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